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(71) Applicant *(for all designated States except US)*: **IM-CLONE SYSTEMS INCORPORATED** [US/US]; 180 Varick Street, New York, NY 10014 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PIATNITSKI, Evgueni** [RU/US]; 868 East 7th Street, Brooklyn, NY 11230 (US). **KISELYOV, Alexander** [UA/US]; 174 Washington Street, Jersey City, NJ 07302 (US). **DOODY, Jacqueline** [US/US]; 94-31 109th Avenue, Ozone Park, NY 11417 (US). **HADARI, Yaron** [IL/US]; 205 East 95th Street, New York, NY 10128 (US). **OUYANG, Shawn** [CN/US]; 2802 Parsons Boulevard, Flushing, NY 11354 (US). **CHEN, Xiaoling** [CA/US]; 1051 73rd Street, Brooklyn, NY 11228 (US).

(74) Agents: **SOMERVILLE, Deborah, A.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

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(54) Title: ANTI-ANGIOGENIC COMPOUNDS AND THEIR USE IN CANCER TREATMENT

(57) Abstract: Compounds that inhibit angiogenesis and are useful in the treatment of angiogenic dependent diseases like cancer are disclosed as well as pharmaceutical compositions that contain such compounds, methods of treating angiogenic dependent diseases and conditions in mammals using such compounds and methods of producing the compounds and compositions.

# ANTI-ANGIOGENIC COMPOUNDS AND
# THEIR USE IN CANCER TREATMENT

5       This application claims priority to U.S. Proviosnal Application No. 60/432,007, filed

December 10, 2002 and to U.S. Patent Application No.(awaited), filed December 4, 2003.


## FIELD OF THE INVENTION

        The present invention relates to novel five-membered ring heterocycles that inhibit

10      the tyrosine kinase activity of VEGF receptors and are useful in the treatment of cancers,

processes for making the heterocycles, pharmaceutical compositions and dosage forms

that contain them, methods of treating angiogenic dependent diseases in mammals using

them, and methods of manufacturing the compositions and dosage forms.


## BACKGROUND OF THE INVENTION

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        Angiogenesis is the process by which new blood vessels develop in an organism.

During angiogenesis, capillary endothelial cells proliferate and migrate from pre-existing

blood vessels into other tissues where they assemble into tubular structures and join to

form tubular assemblies and closed-circuit vascular systems. These vascular systems

20      undergo maturation to form new capillary vessels connected to the vascular network.

        Angiogenesis is important to normal physiological processes like embryonic

development, follicular growth, and wound healing.  Angiogenesis also is necessary to the

progression of some pathological conditions like neoplastic diseases (cancers) and

non-neoplastic diseases that involve abnormal neovascularization like some inflammatory

25      diseases and vascular proliferative diseases like atherosclerosis, restenosis and

neovascular glaucoma  (Folkman, J. and Klagsbrun, M. *Science* 235:442-447 (1987)).  In

neoplastic diseases, the vascularization provides nourishment to the neoplasm and enables

the migration of tumor cells through the vasculature.  Inflammatory diseases whose

progression is accompanied by blood vessel proliferation include rheumatoid arthritis,

30      psoriasis, diabetic retinopathy and age-related macular degeneration.  These and other

pathological conditions that are aggravated by persistent or uncontrolled angiogenesis are known as angiogenic dependent diseases.

5    One means of influencing the progression of angiogenic dependent diseases is to restrict the blood supply to diseased cells.  Occlusion of the blood vessels that supply diseased cells by invasive procedures requires that the site(s) of the diseased cells be identified.  Invasive procedures are generally limited to treatment at a single site, or a small number of sites.  Direct mechanical restriction of blood supply often is ineffective at killing the diseased cells because collateral blood vessels develop, often quite rapidly, restoring the blood supply to the diseased cells.

10    Other approaches to restricting blood supply to tumor cells have focused on the modulation of factors that are involved in the regulation of angiogenesis at the cellular level.  *See e.g.* U.S. Patent No. 6,365,157.  Angiogenesis, like many other biological mechanisms requiring regulation of cellular proliferation, is dependent on the phosphorylation of proteins by protein tyrosine kinases.  Overexpression or aberrations in

15    the pathways coupled to these kinases can produce pathological outcomes  (like uncontrolled angiogenesis and tumor growth).  Inhibitors, modulators or regulators of kinase activity have the potential to be therapeutically relevant agents in the treatment of tumor growth and other angiogenic dependent diseases.

Vascular endothelial growth factor ("VEGF") has been implicated in the regulation

20    of angiogenesis *in vivo* (Klagsbrun, M. and D'Amore, P. (1991) *Annual Rev. Physiol.* 53: 217-239).  VEGF is a homodimeric glycoprotein consisting of two 23 kD subunits.  Four different monomeric isoforms of VEGF resulting from alternative splicing of mRNA have been identified.  These include two membrane bound forms ($VEGF_{206}$ and $VEGF_{189}$) and two soluble forms ($VEGF_{165}$ and $VEGF_{121}$).  $VEGF_{165}$ is the most abundant isoform in all

25    human tissues except placenta.

VEGF is a potent endothelial-cell specific mitogen ($ED_{50}$ 2-10 pM), specifically promoting proliferation of endothelial cells. VEGF is expressed in embryonic tissues (Breier et al., *Development (Camb.)* 114:521 (1992)), macrophages, and proliferating epidermal keratinocytes during wound healing (Brown et al., *J. Exp. Med.*, 176:1375

30    (1992)), and may be responsible for tissue edema associated with inflammation (Ferrara et

al., *Endocr. Rev.* 13:18 (1992)). *In situ* hybridization studies have demonstrated high
levels of VEGF expression in a number of human tumor lines including glioblastoma
multiforme, hemangioblastoma, other central nervous system neoplasms and
AIDS-associated Kaposi's sarcoma (Plate, K. et al. (1992) *Nature* 359: 845-848; Plate, K.

5    et al. (1993) *Cancer Res.* 53: 5822-5827; Berkman, R. et al. (1993) *J. Clin. Invest.* 91:
153-159; Nakamura, S. et al. (1992) *AIDS Weekly*, 13 (1)).  A high level of VEGF
expression also has been found in atherosclerotic lesions, plaques and inflammatory cells.

VEGF mediates its biological effect through high affinity VEGF receptors which
are selectively expressed on endothelial cells during, for example, embryogenesis

10   (Millauer, B., et al. (1993) *Cell* 72: 835-846) and tumor formation.  These receptors
comprise a tyrosine kinase cytosolic domain that initiates the signaling pathway involved
in cell growth.

VEGF receptors are class III receptor-type tyrosine kinases characterized by having
several, typically 5 or 7, immunoglobulin-like loops in their amino-terminal extracellular

15   receptor ligand-binding domains (Kaipainen et al., *J. Exp. Med.*, 178:2077-88 (1993)).
The other two regions include a transmembrane region and a carboxy-terminal intracellular
catalytic domain interrupted by an insertion of hydrophilic interkinase sequences of
variable lengths, called the kinase insert domain (Terman et al., *Oncogene*, 6:1677-83
(1991)).  VEGF receptors include *fms*-like tyrosine kinase receptor (flt-1), or VEGFR-1,

20   sequenced by Shibuya et al., *Oncogene*, 5:519-24 (1990), kinase insert domain-containing
receptor/fetal liver kinase (KDR/flk-1), or VEGFR-2, described in WO 92/14248, filed
February 20, 1992, and Terman et al., *Oncogene*, 6:1677-83 (1991) and sequenced by
Matthews et al., *Proc. Natl. Acad. Sci. USA*, 88:9026-30 (1991), although other receptors
can also bind VEGF.  Another tyrosine kinase receptor, VEGFR-3 (flt-4), binds the VEGF

25   homologues VEGF-C and VEGF-D and is important in the development of lymphatic
vessels.

It is generally believed that KDR/VEGFR-2 is the main VEGF signal transducer
that results in endothelial cell proliferation, migration, differentiation, tube formation,
increase of vascular permeability, and maintenance of vascular integrity.  VEGFR-1

30   possesses a much weaker kinase activity, and is unable to generate a mitogenic response

when stimulated by VEGF, although it binds to VEGF with an affinity that is approximately 10-fold higher than KDR. VEGFR-1 has also been implicated in VEGF and placenta growth factor (PlGF) induced migration of monocytes and macrophages and production of tissue factor.

5          When VEGF is expressed by a tumor mass, endothelial cells adjacent to the VEGF+ tumor cells will up-regulate expression of VEGF receptor molecules, *e.g.*, VEGFR-1 and VEGFR-2.   High levels of VEGFR-2 are expressed by endothelial cells that infiltrate gliomas (Plate, K. et al., (1992) *Nature* 359: 845-848), and are specifically upregulated by VEGF produced by human glioblastomas (Plate, K. et al. (1993) *Cancer*

10         *Res.* 53: 5822-5827).   The finding of high levels of VEGR-2 expression in glioblastoma associated endothelial cells (GAEC) suggests that receptor activity is induced during tumor formation, since VEGFR-2 transcripts are barely detectable in normal brain endothelial cells, indicating generation of a paracrine VEGF/VEGFR loop.  This upregulation is confined to the vascular endothelial cells in close proximity to the tumor.  Blocking VEGF

15         activity with neutralizing anti-VEGF monoclonal antibodies (mAbs) results in inhibition of the growth of human tumor xenografts in nude mice (Kim, K. et al. (1993) *Nature* 362: 841-844), suggesting a direct role for VEGF in tumor-related angiogenesis.

           Accordingly, VEGFR antagonists have been developed to treat vascularized tumors and other angiogenic associated diseases.  These have included neutralizing antibodies that

20         block signaling by VEGF receptors expressed on vascular endothelial cells to reduce tumor growth by blocking angiogenesis through an endothelial-dependent paracrine loop. *See,* *e.g.*, U.S. Patent No. 6,365,157 and International Publications Nos. WO 00/44777, WO 01/54723, WO 01/74296, WO 01/90192, "Bispecific Antibodies That Bind to VEGF Receptors" (Zhu, International PCT application filed June 26, 2002), and "Method of

25         Treating Atherosclerosis and Other Inflammatory Diseases" (Carmeliet et al.; International PCT application filed Jun. 20, 2002).

           VEGF receptors also have been found on some non-endothelial cells, such as tumor cells producing VEGF, wherein an endothelial-independent autocrine loop is generated to support tumor growth.  It has been demonstrated that a VEGF/human VEGFR-2 autocrine

30         loop mediates leukemic cell survival and migration in vivo.  Dias et al., "Autocrine

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stimulation of VEGFR-2 activates human leukemic cell growth and migration," *J. Clin. Invest.* 106:511-521 (2000); Witte et al., "Treatment of non-solid mammalian tumors with vascular endothelial growth factor receptor antagonists;" and International Publication No. WO 01/74296. Similarly, VEGF production and VEGFR expression also have been reported for some solid tumor cell lines in vitro. (*See* Tohoku, Sato, *J. Exp. Med.*, 185(3): 173-84 (1998); Nippon, *Sanka Fujinka Gakkai Zasshi,*:47(2): 133-40 (1995); and Ferrer, FA, *Urology*, 54(3):567-72 (1999)). It has further been demonstrated that VEGFR-1 Mabs inhibit an autocrine VEGFR/human VEGFR-1 loop in breast carcinoma cells. Wu, et al., "Monoclonal antibodys against VEGFR1 inhibits flt1-positive DU4475 human breast tumor growth by a dual mechanism involving anti-angiogenic and tumor cell growth inhibitory activities," AACR_NCI_EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 29-November 2, 2001, Abstract #7; and Carmeliet et al. (International PCT application filed June 20, 2002).

In view of the foregoing, it will be appreciated that inhibitors of VEGF receptor tyrosine kinase activity can interrupt the paracrine and/or autocrine VEGF/ VEGFR loop. Such inhibitors hold the potential to disrupt pathological angiogenisis and influence the progression of angiogenic dependent diseases.

Accordingly, there is a need for inhibitors of VEGF receptor tyrosine kinase activity. However, the road from the discovery that a compound is an inhibitor of VEGF receptor tyrosine kinases to the development of effective therapeutic agents against pathogenic vascularization is uncertain. Many factors impinge upon the outcome whether a compound shown to be effective in *in vitro* experiments will be an effective therapeutic agent against cancer. Such factors include side effects caused by administration of the compound in dosages necessary for anti-angiogenic effectiveness, the cost of producing or obtaining the compound, the method by which the compound must be administered and many others.

It would be highly desirable to have available new candidate therapeutic compounds with VEGF receptor tyrosine kinase activity, that are storage stable and preparable by multi-step chemical synthesis from commercially available or readily accessible starting materials.

## SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide active agents capable of inhibiting the tyrosine kinase activity of vascular endothelial cells, in particular vascular endothelial cells adjacent to cells affected by a disease that needs

5  neovascularization in order to advance to a life threatening stage. It is a further object of the invention to provide agents that are useful for the treatment of cancer. Novel small molecules have been discovered which have an inhibitory effect on the tyrosine kinase activity of VEGFR-2 receptors and utility in cancer treatment. These compounds share a 1,3-disubstituted five-membered heterocyclic ring scaffold represented by Formula (I):

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(I)

wherein :

$X_1$ and $X_2$ are atoms or radicals independently selected from the group consisting of

15  oxygen, sulfur, nitrogen, radicals of formula C-$R_3$ and radicals of formula N-$R_3$, with the proviso that at least one of $X_1$ and $X_2$ is oxygen, sulfur, nitrogen or a diradical of formula N-$R_3$, wherein:

R$_3$ is an atom or radical selected from the group consisting of:

1)      hydrogen,

20     2)      halogen,

3)      alkyl, optionally substituted with one or more substituents selected from $R_4$;

4)      alkenyl, optionally substituted with one or more substituents selected from $R_4$;

5) alkynyl, optionally substituted with one or more substituents selected from $R_4$;

wherein $R_4$ is an atom or radical selected from the group consisting of:

a) halogen;

b) alkyl, which may be optionally substituted with one or more halogen, hydroxy or lower alkoxy;

c) alkenyl, which may be optionally substituted with one or more halogen, hydroxy or lower alkoxy;

d) nitro;

e) cyano;

f) oxo;

g) vinyl;

h) styryl;

i) a group of formula $-C(O)R_5$, $-CO_2R_5$, $-OR_5$, $-SR_5$, $-SOR_5$, $-SO_2R_5$, $-NR_5R_6$, $-NCO_2R_5$, or $-OCO_2R_5$ where $R_5$ and $R_6$ are atoms or radicals independently selected from the group consisting of hydrogen, lower alkyl, aralkyl, aryl and heteroaryl;

$X_3$ is selected from the group consisting of oxygen, sulfur, nitrogen and diradicals of formula $N-R_3$,

$Y_1$ and $Y_2$ are atoms independently selected from the group consisting of nitrogen and carbon,

$R_1$ is a radical selected from the group consisting of:



and

,

wherein $W_1$ is nitrogen or $C-R_{w1}$, $W_2$ is nitrogen or $C-R_{w2}$, $W_3$ is nitrogen or $C-R_{w3}$, $W_4$ is nitrogen or $C-R_{w4}$, $W_5$ is nitrogen or $C-R_{w5}$, $W_6$ is nitrogen or

C-$R_{w6}$, $W_7$ is nitrogen or C-$R_{w7}$, $W_1$ is nitrogen or C-$R_{w8}$ and $W_9$ is nitrogen or C-$R_{w9}$ , each $R_{w1}$, $R_{w2}$, $R_{w3}$, $R_{w4}$, $R_{w5}$, $R_{w6}$, $R_{w7}$, $R_{w8}$ and $R_{w9}$ being an atom or radical independently selected from the group consisting of:

1)      hydrogen,

2)      halogen,

3)      nitro,

4)      cyano,

5)      alkyl, optionally substituted with one or more substituents selected from $R_4$,

6)      alkenyl, optionally substituted with one or more substituents selected from $R_4$,

7)      alkynyl, optionally substituted with one or more substituents selected from $R_4$,

8)      aralkyl, optionally substituted with one or more substituents selected from $R_4$,

9)      phenyl, optionally substituted with 1 to 5 substituents selected from $R_4$,

10)      a group of the formula -$CO_2R_5$, -$COR_5$, -$OR_5$, -$SR_5$, -$SOR_5$, -$SO_2R_6$, -$NR_5R_6$,

11)      pyridyl, optionally substituted with 1 to 4 substituents selected from $R_4$,

12)      pyrazinyl, optionally substituted with 1 to 3 substituents selected from $R_4$,

13)      pyrimidinyl, optionally substituted with 1 to 3 substituents selected from $R_4$,

14)      indazolyl, optionally substituted with 1 to 5 substituents selected from $R_4$,

15)      tetrazolyl, and

14)      heterocyclic radicals of formulae:

wherein $X_4$ is O, S, or N-$R_4$,

　　　　　　　$a$ is 0 to 3,

　　　　　　　$b$ is 0 to 2,

　　　　　　　$c$ is 0 or 1, or

together, one or more of the combinations $R_{w1}$ and $R_{w2}$, $R_{w2}$ and $R_{w3}$, $R_{w3}$ and $R_{w4}$, $R_{w5}$ and $R_{w6}$, $R_{w6}$ and $R_{w7}$, $R_{w7}$ and $R_{w8}$, and $R_{w8}$ and $R_{w9}$ form a fused 5- or 6- membered carbocyclic ring or heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen and sulfur,

Z is selected from the group consisting of oxygen, sulfur, -S(O)-, -S(O)$_2$-, -$CR_5R_6$-, -$CR_5R_6O$-, $CR_5R_6NR_3$- and -$NR_3$-

$R_2$ is a radical of formula -$OR_{7a}$, -$SR_{7a}$, -$S(O)R_{7a}$, -$CR_5R_6R_{7a}$, -$CR_5R_6$-$OR_{7a}$

　　　　wherein $R_{7a}$ is a radical selected from the group consisting of:

　　　　1)　　　-$CH_2$-$R_8$,

　　　　2)　　　-$CH_2CH_2$-$R_8$,

　　　　3)　　　-$CH_2CH_2CH_2$-$R_8$, and

　　　　4)　　　-$R_8$,

　　　　　　　wherein $R_8$ is a cyclic radical selected from the group consisting of:

　　　　a)　　　aromatic carbocyclic radicals, optionally substituted with 1 to 5 substituents wherein the substituents are selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$, and

　　　　b)　　　aromatic and non-aromatic heterocyclicyl radicals, optionally substituted with 1 to 5 substituents wherein the substituents are either selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic

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ring optionally substituted with one or more substituents

selected from $R_4$, or

$R_2$ is a radical selected from the group consisting of $-CR_5R_6NR_{7a}R_{7b}$, and $-NR_{7a}R_{7b}$

and:

$R_{7a}$ and $R_{7b}$ are both hydrogen,

$R_{7a}$ and $R_{7b}$ together form a 6 membered ring heterocycle, optionally

substituted with one or more substituents selected from the group $R_4$, or

$R_{7b}$ is hydrogen or a radical selected from $R_4$ and $R_{7a}$ is a radical selected

from the group consisting of:

1)      $-CH_2-R_8$,

2)      $-CH_2CH_2-R_8$,

3)      $-CH_2CH_2CH_2-R_8$, and

4)      $-R_8$,

wherein $R_8$ is a cyclic radical selected from the group consisting of:

a)      aromatic carbocyclic radicals, optionally substituted with 1

to 5 substituents wherein the substituents are selected from

$R_4$ or two adjacent substituents can form a 5, 6 or 7

membered fused carbocyclic or heterocyclic ring optionally

substituted with one or more substituents selected from $R_4$,

and

b)      aromatic and non-aromatic heterocyclicyl radicals, optionally

substituted with 1 to 5 substituents wherein the substituents

are either selected from $R_4$ or two adjacent substituents can

form a 5, 6 or 7 membered fused carbocyclic or heterocyclic

ring optionally substituted with one or more substituents

selected from $R_4$.

Processes for preparing the active agents are also provided. The active agents may

be incorporated into pharmaceutical compositions and dosage forms in accordance with

further teachings of this disclosure. The active agents, compositions and dosage forms

may be used independently or together to treat angiogenic dependent diseases according to the method aspect of the invention.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

Unless otherwise indicated, chemical terms used in this disclosure have the meaning attributed to them by those skilled in the art of medicinal and organic chemistry and biological terms have the meaning attributed to them by those skilled in the art of molecular and cell biology. The following express definitions are consonant with those understandings.

A "hydrocarbyl" radical means a fragment of a molecule that contains carbon and hydrogen. As used in this disclosure, the term is intended to include fragments that contain, in addition to carbon and hydrogen, any number of heteroatoms. Heteroatoms may be pendant, such as the carbonyl oxygen of acetone or the fluorine atoms of 2,2-difluoropropane. Heteroatoms also may be incorporated into a hydrocarbyl fragment, such as the nitrogen of N,N-dimethylaminomethyl, the oxygen atom of diethyl ether or a polyethyleneglycol fragment.

The term "alkyl" as used herein refers to a saturated hydrocarbyl radical that may be unsubstituted or substituted with one or more substituents. The alkyl radical may be straight, branched or cyclic. The term "lower alkyl" is reserved for alkyl radicals containing from 1 to 6 carbon atoms. Linear and branched lower alkyl substituents include methyl, ethyl, propyl, isopropyl, butyl and t-butyl, and the like. Cyclic lower alkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkenyl" as used herein refers to a straight, branched or cyclic non-aromatic hydrocarbyl radical containing at least one carbon to carbon double bond. The term "lower alkenyl" as used herein is reserved for an alkenyl radical containing from 2 to 6 carbon atoms. Lower alkenyl groups include ethenyl, propenyl, butenyl cyclohexenyl, and the like.

The term "alkynyl" as used herein refers to a straight, branched or cyclic hydrocarbyl radical containing at least one carbon to carbon triple bond. The term "lower alkynyl" as used herein is reserved for an alkynyl radical containing from 2 to 6 carbon atoms. Lower alkynyl groups include ethynyl, propynyl and butynyl, and the like.

Alkyl, alkenyl and alkyl radicals typically have between 1 and 40 carbon atoms.

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The term "aryl" as used herein refers to carbocyclic and heterocyclic radicals that are "aromatic," *i.e.* they possess cyclic π electron systems that have a stabilizing electronic character called resonance stabilization. Fieser & Fieser, *Organic Chemistry* 525-526 (3rd ed. 1956), Streitweiser, A.; Heathcock, C.H. *Introduction to organic Chemistry* 643 (2nd ed. 1981). Aryl radicals can be distinguished by those skilled in the art from other radicals having cyclic π electron systems by applying the Huckel rule which states that resonance stabilization will occur when the number of electrons that are delocalized in the π electron system is 4n+2 where n is an integer. Aryl radicals include unsubstituted or substituted 6-membered aromatic rings, such as, phenyl, substituted phenyl and like, as well bicyclic rings, such as naphthyl, and polycyclic rings, such as anthracenyl, and heterocyclic radicals, such as pyridinyl as well as, imidazolyl, oxazolyl, thiazolyl, indazolyl and the like (wherein the Huckel rule is satisfied by the contribution by a heteroatom of a pair of electrons to the aromatic stabilization).

The terms "heterocycle," "heteroaryl" and "heterocyclic" mean a stable 5- to 6-membered mono- or 7- to 10-membered fused bicyclic ring system, any ring of which may be saturated or unsaturated, aromatic or non-aromatic, provided that from one to three ring atoms are selected from the heteroatoms N, O and S while the other ring atoms are carbon. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized.

The term "heterocycles" includes the abovementioned heteroaryls, as well as reduced (*e.g.* dihydro and tetrahydro) analogs thereof. Heterocycles include any bicyclic group in which any of the above-defined rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom, which results in the creation of a stable structure. Examples of such heterocyclic components include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl,

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tetrahydropyranyl, thiophenyl, imidazopyridinyl, tetrazolyl, triazinyl, thienyl, benzothienyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl.

The term "alkoxy" refers to a radical containing a straight, branched or cyclic hydrocarbyl radical attached via an oxygen atom. Substituents on the hydrocarbyl group

5      may include for example, a phenyl ring, in which the alkoxy may be for example, a benzyloxy group. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, vinyloxy, and the like.

The term "aralkyl" as used herein contemplates a lower alkyl group which has as a

10      substituent an aryl group.

The term "halo" or "halogen" as used herein is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The chemical nomenclature used in this disclosure follows the system for naming compounds of the International Union of Pure and Applied Chemistry (IUPAC). The

15      IUPAC system assigns a number to every atom in a compound. This disclosure also uses relative numbering where it is the clearest way to describe the invention to those skilled in the art. The absolute numbering assigned by the IUPAC system is to be distinguished from relative numbering commonly used to express bonding relationships between functional groups. Thus, it will be appreciated that the phenyl groups of 3,5-diphenyl-1,2,4-triazole

20      are in a 1,3 relationship to each other because they are separated by three atoms including those to which they are attached. Whether atom numbering is absolute or relative will be clear to one skilled in the art from the context in which it is used.

When one or more chiral centers are present in the compounds of the present invention, the individual isomers and mixtures thereof (e.g., racemates, etc.) are intended

25      to be encompassed by the formulae depicted herein.

### 1,3-Disubstituted Five-membered Ring Heterocyclic VEGF Tyrosine Kinase Inhibitors

The present invention provides novel compounds that inhibit tyrosine kinase activity of vascular endothelial growth factor receptors. The present invention is not

30      intended to be limited to any particular mechanism of VEGF receptor kinase inhibition.

The compounds of the present invention are certain appropriately 1,3-disubstituted five-membered ring heterocycles that are encompassed by Formula (I).



(I)

wherein :

$X_1$ and $X_2$ are atoms or radicals independently selected from the group consisting of oxygen, sulfur, nitrogen, radicals of formula $C$-$R_3$ and radicals of formula $N$-$R_3$, with the proviso that at least one of $X_1$ and $X_2$ is oxygen, sulfur, nitrogen or a diradical of formula $N$-$R_3$, wherein:

R_3 is an atom or radical selected from the group consisting of:

1)      hydrogen,

2)      halogen,

3)      alkyl, optionally substituted with one or more substituents selected from $R_4$;

4)      alkenyl, optionally substituted with one or more substituents selected from $R_4$;

5)      alkynyl, optionally substituted with one or more substituents selected from $R_4$;

wherein $R_4$ is an atom or radical selected from the group consisting of:

a)      halogen;

b)      alkyl, which may be optionally substituted with one or more halogen, hydroxy or lower alkoxy;

c)      alkenyl, which may be optionally substituted with one or more halogen, hydroxy or lower alkoxy;

d)      nitro;

e)      cyano;

f)      oxo;

g)      vinyl;

h)      styryl;

i)      a group of formula $-C(O)R_5$, $-CO_2R_5$, $-OR_5$, $-SR_5$, $-SOR_5$, $-SO_2R_5$, $-NR_5R_6$, $-NCO_2R_5$, or $-OCO_2R_5$ where $R_5$ and $R_6$ are atoms or radicals independently selected from the group consisting of hydrogen, lower alkyl, aralkyl, aryl and heteroaryl;

$X_3$ is selected from the group consisting of oxygen, sulfur, nitrogen and diradicals of formula $N-R_3$,

$Y_1$ and $Y_2$ are atoms independently selected from the group consisting of nitrogen and carbon,

$R_1$ is a radical selected from the group consisting of:



wherein $W_1$ is nitrogen or $C-R_{w1}$, $W_2$ is nitrogen or $C-R_{w2}$, $W_3$ is nitrogen or $C-R_{w3}$, $W_4$ is nitrogen or $C-R_{w4}$, $W_5$ is nitrogen or $C-R_{w5}$, $W_6$ is nitrogen or $C-R_{w6}$, $W_7$ is nitrogen or $C-R_{w7}$, $W_1$ is nitrogen or $C-R_{w8}$ and $W_9$ is nitrogen or $C-R_{w9}$ , each $R_{w1}$, $R_{w2}$, $R_{w3}$, $R_{w4}$, $R_{w5}$, $R_{w6}$, $R_{w7}$, $R_{w8}$ and $R_{w9}$ being an atom or radical independently selected from the group consisting of:

1)      hydrogen,

2)      halogen,

3)      nitro,

4)      cyano,

5) alkyl, optionally substituted with one or more substituents selected from $R_4$,

6) alkenyl, optionally substituted with one or more substituents selected from $R_4$,

7) alkynyl, optionally substituted with one or more substituents selected from $R_4$,

8) aralkyl, optionally substituted with one or more substituents selected from $R_4$,

9) phenyl, optionally substituted with 1 to 5 substituents selected from $R_4$,

10) a group of the formula $-CO_2R_5$, $-COR_5$, $-OR_5$, $-SR_5$, $-SOR_5$, $-SO_2R_6$, $-NR_5R_6$,

11) pyridyl, optionally substituted with 1 to 4 substituents selected from $R_4$,

12) pyrazinyl, optionally substituted with 1 to 3 substituents selected from $R_4$,

13) pyrimidinyl, optionally substituted with 1 to 3 substituents selected from $R_4$,

14) indazolyl, optionally substituted with 1 to 5 substituents selected from $R_4$,

15) tetrazolyl, and

14) heterocyclic radicals of formulae:

$$\underset{(R_4)_a}{\Longleftrightarrow}X_4 \quad \underset{(R_4)_b}{\Longleftrightarrow}X_4 \quad \underset{(R_4)_b}{\Longleftrightarrow}X_4 \quad \underset{(R_4)_c}{\Longleftrightarrow}X_4 \quad \underset{(R_4)_c}{\Longleftrightarrow}X_4 \quad \underset{(R_4)_c}{\Longleftrightarrow}X_4 \quad \underset{(R_4)_c}{\Longleftrightarrow}X_4$$

wherein $X_4$ is O, S, or N-$R_4$,

a is 0 to 3,

b is 0 to 2,

c is 0 or 1, or

together, one or more of the combinations $R_{w1}$ and $R_{w2}$, $R_{w2}$ and $R_{w3}$, $R_{w3}$ and $R_{w4}$, $R_{w5}$ and $R_{w6}$, $R_{w6}$ and $R_{w7}$, $R_{w7}$ and $R_{w8}$, and $R_{w8}$ and $R_{w9}$ form a

fused 5- or 6- membered carbocyclic ring or heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen and sulfur,

Z is selected from the group consisting of oxygen, sulfur, $-S(O)-$, $-S(O)_2-$, $-CR_5R_6-$, $-CR_5R_6O-$, $CR_5R_6NR_3-$ and $-NR_3-$

$R_2$ is a radical of formula $-OR_{7a}$, $-SR_{7a}$, $-S(O)R_{7a}$, $-CR_5R_6R_{7a}$, $-CR_5R_6-OR_{7a}$

wherein $R_{7a}$ is a radical selected from the group consisting of:

1)      $-CH_2-R_8$,

2)      $-CH_2CH_2-R_8$,

3)      $-CH_2CH_2CH_2-R_8$, and

4)      $-R_8$,

wherein $R_8$ is a cyclic radical selected from the group consisting of:

a)      aromatic carbocyclic radicals, optionally substituted with 1 to 5 substituents wherein the substituents are selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$, and

b)      aromatic and non-aromatic heterocyclicyl radicals, optionally substituted with 1 to 5 substituents wherein the substituents are either selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$, or

$R_2$ is a radical selected from the group consisting of $-CR_5R_6-NR_{7a}R_{7b}$, and $-NR_{7a}R_{7b}$ and:

$R_{7a}$ and $R_{7b}$ are both hydrogen,

$R_{7a}$ and $R_{7b}$ together form a 6 membered ring heterocycle, optionally substituted with one or more substituents selected from the group $R_4$, or

$R_{7b}$ is hydrogen or a radical selected from $R_4$ and $R_{7a}$ is a radical selected from the group consisting of:

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1)      -CH$_2$-R$_8$,

2)      -CH$_2$CH$_2$-R$_8$,

3)      -CH$_2$CH$_2$CH$_2$-R$_8$, and

4)      -R$_8$,

wherein R$_8$ is a cyclic radical selected from the group consisting of:

a)      aromatic carbocyclic radicals, optionally substituted with 1 to 5 substituents wherein the substituents are selected from R$_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from R$_4$, and

b)      aromatic and non-aromatic heterocyclicyl radicals, optionally substituted with 1 to 5 substituents wherein the substituents are either selected from R$_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from R$_4$.

Generally, substituent R$_2$ is preferably a radical of formula -NH-R$_8$, -NHCH$_2$-R$_8$, -NHCH$_2$CH$_2$-R$_8$ or -NHCH$_2$CH$_2$CH$_2$-R$_8$, wherein R$_8$ is an optionally substituted phenyl radical, optionally substituted bicyclic aromatic carbocyclic radical, optionally substituted polycyclic aromatic carbocyclic  radical, optionally substituted monocyclic aromatic heterocyclic radical, optionally substituted bicyclic aromatic heterocyclic radical or optionally substituted polycyclic aromatic heterocyclic radical.  Preferred R$_8$ substituents are phenyl, optionally substituted with 1 to 5 substituents selected from R$_4$; pyridinyl, optionally substituted with 1 to 4 substituents selected from R$_4$; pyrazinyl, optionally substituted with 1 to 3 substituents selected from R$_4$; pyrimidinyl, optionally substituted with 1 to 3 substituents selected from R$_4$; indazolyl, optionally substituted with 1 to 5 subsitutents selected from R$_4$; tetrazolyl; or an aromatic heterocyclic radical of formula:

wherein X, $R_4$ and a-c are as previously defined. An especially preferred Z substituent is NH.

Compounds of Formula (I) were previously unknown in any state of purity and are not a known component of any naturally occurring composition. Thus, the present invention is directed to these compounds in all states of purity. The compounds of this invention exist in different physical states as well, such as dissolved states and condensed states. Condensed states include salts and solvates of the compound (particular salts suitable for pharmaceutical use are described below). The present invention also relates to "prodrugs" of compounds of Formula (I). A "pro-drug" is a compound that is administered to a patient and is converted within the patient's body into a second compound that exerts a therapeutic effect. The present invention encompasses pro-drugs that are transformed *in vivo* to yield the Formula (I) compound or a protein conjugate of it. Pro-drugs are thoroughly discussed in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

The VEGF receptor antagonists of the invention are readily prepared by general methodologies described in compendia and treatises on heterocycles and organic synthesis methods. In particular, there may be mentioned *Comprehensive Heterocyclic Chemistry* (Alan Katritzky and Charles Rees eds., Pergamon Press: Oxford 1984); *Heterocyclic Compounds* (John Wiley & Sons: New York 1981) and *Methoden der Organishchen Chemie* (Houben-Weyl:Stuttgart 1974). Any heterocyclic ring systems encompassed by Formula (I) that are inaccessible because they are unstable can be readily determined by those skilled in the art by consulting standard reference works in the field such as those referenced immediately above.

<u>1,2,4-Triazole VEGF Tyrosine Kinase Inhibitors</u>

One preferred class of 1,3-disubstituted (relative numbering) five-membered ring heterocycles of Formula (I) are 3,5-disubstituted-1,2,4-triazoles. Triazoles are 5-membered ring heterocycles containing three nitrogen atoms. Triazoles exist in two distinct classes–1,2,3-triazoles and 1,2,4-triazoles--differentiated by the positions of the nitrogen atoms in the aromatic ring. Both classes have aromatic character. 1,2,3-Triazoles characteristically have a annular nitrogen atom bonded to two other annular nitrogen atoms. The 1,2,4-triazoles characteristically have only one direct bond between annular nitrogen atoms. The triazoles that have been discovered to have VEGF receptor kinase inhibitory activity are 1,2,4-triazoles. Accordingly, one preferred class of 1,2,4-triazoles of the present invention are those that are encompassed by Formula (Ia):
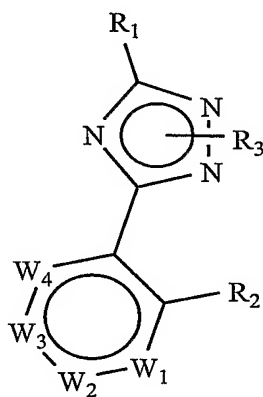


(Ia)

wherein $R_1$, $R_2$, $R_3$, $W_1$, $W_2$, $W_3$ and $W_4$ are as previously defined with respect to Formula (I).

In preferred 1,2,4-triazoles of the present invention, $R_3$ is hydrogen. In yet more preferred 1,2,4-triazoles of the present invention, $R_2$ is -NH-$R_{7a}$, $R_3$ is hydrogen, $W_2$ is C-$R_{w2}$, $W_3$, $W_4$, $W_5$ and $W_9$ are CH, $W_7$ is C-$R_{w7}$ and $W_8$ is C-$R_{w8}$. Accordingly, more preferred 1,2,4-triazoles of the present invention are those encompassed by Formula (Ia'):

(Ia').
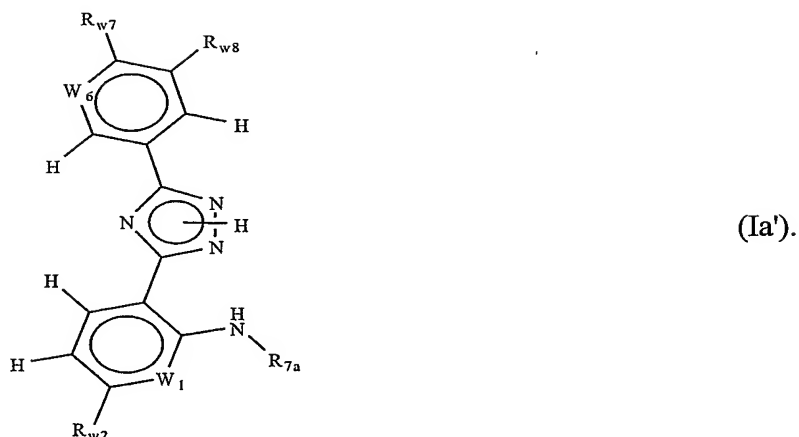
wherein $W_1$, $W_6$, $R_{w2}$, $R_{w7}$, $R_{w8}$ and $R_{7a}$ are as previously defined with respect to Formula (I).

5        In a second preferred group of 1,2,4-triazoles of the present invention, the triazole ring and one of the aryl rings are connected through a linking group Z. In addition, $R_2$ is a radical of formula -$NR_{7a}R_{7b}$. Accordingly, this second preferred class of 1,2,4-triazoles is encompassed by Formula (Ia"):



(Ia")
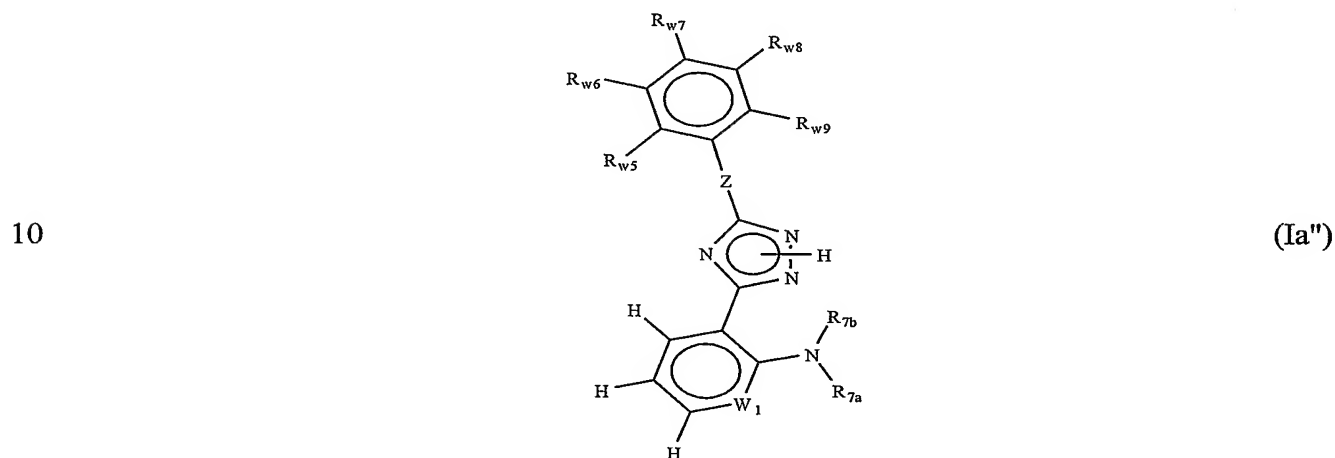
wherein $W_1$, $R_{w5}$-$R_{w9}$, $R_{7a}$, $R_{7b}$ and Z are as previously defined with respect to Formula (I). Yet more preferred 1,2,4-triazoles of Formula (Ia") are those wherein Z is -NH-, -$CH_2O$-, or -$CH_2$-.

15        1,2,4-Triazoles whose annular nitrogens are unsubstituted as they are in Formulae (Ia') and (Ia") are likely to exist as a rapidly equilibrating mixture of three isomers, a

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phenomenon called prototropy. In fact, it has been stated that the parent compound 1,2,4-triazole is best represented as a proton associated with a resonance stabilized triazole anion. Ainsworth et al. *J. Med. Pharm. Chem.* **1962**, *5*, 383. Representations of the three isomers, or tautomers, may be generated by attaching the hydrogen atom whose point of

5        attachment is unspecified to each of the annular nitrogen atoms and adjusting the positions of the two double bonds to obtain proper valency. In the general case, these tautomers are not separable at ambient temperature. All three interconverting tautomers are intended to be covered by Formulae (I), (Ia') and (Ia''), it being understood by those skilled in the art that, when prototropy occurs, one tautomer does not exist free of the other tautomers under

10       conditions in which the compounds of the present invention will be used, *e.g.* in a pharmaceutical composition or the bloodstream of a mammal.

1,2,4-Triazoles are readily prepared by methods described in *Comprehensive Heterocyclic Chemistry* Part 4a (Alan Katritzky and Charles Rees eds., Pergamon Press: Oxford 1984); *Heterocyclic Compounds* Vol. 37 (John Wiley & Sons: New York 1981)

15       and *Methoden der Organishchen Chemie* (Houben-Weyl:Stuttgart 1974).

1,2,4-Triazoles can be prepared from acyclic starting materials by reacting a substituted or unsubstituted hydrazine with certain compounds containing a (-C(=O)-NH-) or -C(=NH)-NH- fragment. Methodologies for making 1,2,4-triazoles from acyclic starting materials include (1) condensation of a hydrazine (R-NHNH$_2$) with an imide

20       (R'–C(O)NHC(O)-R''), known as the Einhorn-Brunner reaction. Einhorn et al. *Liebigs Ann. Chem.* **1905**, *343*, 229; Brunner *Ber. Dtsch Chem. Ges.* **1914**, *47* 2671; Brunner *Mh. Chem.* **1915**, *36*, 509. Additional methodologies include (2) condensation of a hydrazide (a.k.a. acylhydrazine) (R-C(O)NHNH$_2$) with a primary amide (R'C(O)NH$_2$), known as the Pellizzari reaction (3) condensation of an amidrazone (RC(=NH)NR'-NH$_2$) with a

25       carboxylic acid (R''COOH) and (4) cyclization of an acylamidrazone (RC(O)-NR'-N=C(R'')NH$_2$).

Conversion of these compounds to 1,2,4-triazoles is generally performed in a polar organic solvent, like a lower alcohol or THF, under neutral or mildly basic conditions at a concentration of about 1mM to about 2 M. Depending upon the choice of solvent,

30       concentration and nature of the particular starting materials, the reaction may proceed at

reduced, ambient or elevated temperatures. Generally, reaction conditions of about 1M in refluxing anhydrous ethanol may be tried as a starting point for optimization of any particular ring closing reaction. Ethanol may be replaced with a high boiling solvent if the reaction does not proceed at a practicable rate. The Pellizzari reaction suffers in

5        comparison to some of the other methods because high reaction temperatures are frequently required.

In a preferred process, the 1,2,4-triazoles of this invention are prepared by contacting a hydrazide of Formula (II)

10                                                                                        (II)

or salt thereof, with an amidine of Formula (III)

                                                                                         (III)

15

or salt thereof under conditions effective to condense the hydrazide group of (II) and amidine group of (III) into a 1,2,4-triazole ring. The ring closure is effected under basic conditions which can be established using a strong base, with alkali metal hydroxides and alkoxides being preferred. Other bases that may suitable include sodium carbonate,

20       potassium carbonate, sodium bicarbonate, potassium bicarbonate, trialkylamines, such as trimethylamine and triethylamine, dialkylanilines, such as N,N-diethylaniline, pyridines, such as 2,4,6-trimethylpyridine, pyridine, and dimethylaminopyridine, DBU, or DABCO, The molar amount of the base to be used is 1 to 20, preferably 1 to 5, times the amount of limiting reagent.

25       Compounds (II) and (III) can be contacted in a melt (if at least one is a liquid at the reaction temperature) or in an inert diluent. Diluents include water and organic

compounds that are liquid at ambient temperature like certain lower alcohols, such as
methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol and *iso*-butanol; aliphatic
and aromatic hydrocarbons, such as hexane, petroleum ether, benzene, toluene, and xylene;
halogenated hydrocarbons, such as dichloromethane, chloroform and Freons; ethers, such
as diethyl ether, methyl *t*-butyl ether, 1,2-dimethoxyethane, dioxane and tetrahydrofuran;
N,N-dialkyl amides, such as dimethylformamide and dimethylacetamide; ketones, such as
acetone and methyl ethyl ketone; nitriles, such as acetonitrile and acrylonitrile; and
sulfoxides, such as dimethylsulfoxide. Preferably, compounds (II) and (III) are contacted
in a lower alcohol diluent, with a preferred lower alcohol being ethanol.

Conveniently, the ring closure is conducted in a lower alcohol using an alkali metal
salt of the corresponding alkoxide anion or different alkoxide anion as base. Although any
concentration that allows the ring closure to go substantially to completion is suitable, a
concentration of from about 100 mM to about 2 M, more particularly about 1 M, is
recommended. If the reaction does not go to completion in a practicable period of time at
the boiling temperature of the alcohol in the recommended concentration ranges then the
reaction mixture can be concentrated and the residue taken up in a higher boiling solvent,
like chlorobenzene.

Alternatively, it may be desirable for functional group compatibility to prepare a
hydrazide of Formula (IV)

$$\underset{O}{\overset{R_1}{\bigwedge}} NHNHR_3 \qquad (IV)$$
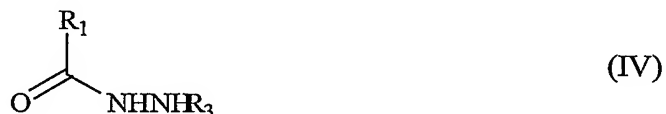
or salt thereof, and an amidine of Formula (V)

$$(V)$$

or salt thereof and react them under generally the same conditions used when reacting (II)
and (III).

The hydrazides and amidines, in turn, may be prepared conventionally by known synthetic pathways. Scheme I depicts a process whereby commercially available and readily accessible nitriles may be converted into an amidine (III) salt that can be used in the making of the 1,2,4-triazoles of this invention. In an anhydrous lower alcohol solvent (*e.g.*

5    ethanol) an appropriately substituted nitrile undergoes addition by a molecule of solvent when treated with anhydrous hydrochloric acid to form an imidate. The imidate may be conveniently isolated as an acid addition salt with the acid catalyst. The imidate salt may be carried forward in the next step of the process. Treatment of the imidate or imidate salt with ammonia transforms the imidate group into an amidine group.

10

<u>Scheme I</u>



(III)
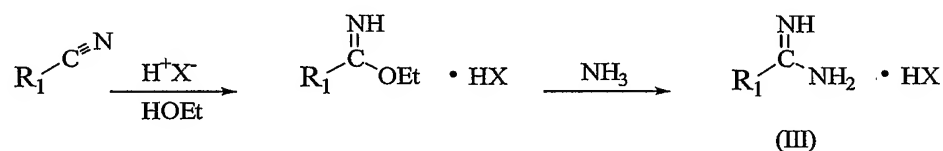
15    *Ortho*-alkylamino substituted benzoic acid hydrazides can be prepared by condensation of an ester of anthranilic acid and a lower alcohol with an aldehyde followed by reduction of the so-formed imine. The resulting *ortho*-methylamino substituted benzoic acid is then contacted with hydrazine to yield hydrazide (II), as shown in Scheme II.

20    <u>Scheme II</u>



(II)
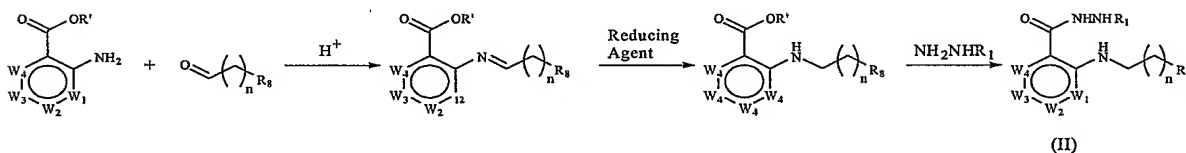
To form the intermediate imine, the aldehyde and anthranilic acid lower alcohol

25    ester are contacted under mildly acidic conditions. Preferred acid catalysts are acetic acid, methanesulfonic acid, trifluoroacetic acid, pivalic acid, hydrochloric acid, hydrobromic acid, with the most preferred acid being acetic acid. After formation of the imine, optionally with isolation, the imine group is reduced with a suitable reducing agent.

Suitable reducing agents include sodium cyanoborohydride, sodium borohydride, lithium aluminum hydride, DIBAL, diborane and the like and catalytic reducing agents such as Raney nickel, and palladium on carbon. The most preferred reducing agent is sodium cyanoborohydride. Additional reducing agents that are known to reduce imines to amines

5       can be found in Larock R.C. *Comprehensive Organic Transformations* 2nd ed. (Wiley-VCH: New York 1999). The addition-elimination and reduction can both be performed in lower alcohols, as wells as ethers and halogenated organic solvents that will solubilize the reactants and reagents that are adapted for use in homogenous liquid phase reactions.

Hydrazide (II) may be prepared by reacting the carboxylic acid group of the

10      reduced product with a hydrazine. Unsubstituted hydrazine is conveniently available as a solid hydrate (Ald. Cat. Nos. 22,581-9 and 20,794-2) and in solutions in THF and water (Ald. Cat. Nos. 43,363-2 and 30,940-0). Substituted hydrazines may be readily prepared from $NH_2NH_2$ by methods well known to those skilled in the art.

Alternatively, it may be possible with some starting materials to prepare the 1,2,4-

15      triazole in a reasonable yield in a one pot process by heating an appropriately substituted nitrile with a benzene hydrazide. *See,* Weidinger, H.; Kranz, J. *Berichte* **1963**, *96*, 1064. However, its lack of general applicability makes it a less preferred process.

Generally, the ring-forming condensation proceeds cleanly and in good yield without protection when *ortho*-secondary amines are present on (V). However,

20      compounds (II)-(V) may bear functionality that inhibits one or more reactions used in making the compounds of the present invention. Compounds (II)-(V) may be derivatized to a form that modifies interfering chemical functionality using well established techniques of functional group protection. For instance, if necessary, hydroxy groups, carboxylic acids, and primary and secondary amine groups on substituents $R_{1-3}$ may be protected as

25      desired as silyl ethers, esters, carbamates, carbonates and the like using techniques well known to the skilled artisan. The selection, application and removal of protective groups are the subjects of many reference works such as Green & Wuts, *Protective Groups in Organic Synthesis* (John Wiley & Sons: New York 1999) and McOmie, *Protective Groups in Organic Chemistry* (Plenum Press: London 1973). The use of protection

30      strategies to make compounds of other heterocyclic classes discussed below also may be

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advantageous.


### 1,3,4-Oxadiazole VEGF Tyrosine Kinase Inhibitors

A second preferred class of 1,3-disubstituted five-membered ring heterocycles of
Formula (I) is 2,5-disubstituted oxadiazoles. Oxadiazoles are 5-membered ring
heterocycles containing two double bonds, one oxygen atom and two nitrogen atoms.
Oxadiazoles are potentially capable of existing in three distinct classes, 1,2,3-, 1,2,4-,
1,3,4- and 1,2,5-oxadiazoles. However, few unfused 1,2,3-oxadiazoles are stable.
Especially preferred oxadiazoles of the present invention are 1,3,4-triazoles. Accordingly,
one preferred class of 1,3-disubstituted five-membered ring heterocycles of the present
invention are those that are encompassed by Formula (Ib)



(Ib)
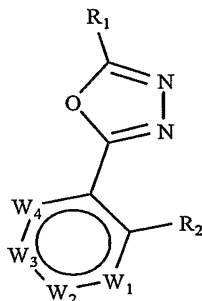
wherein $R_1$, $R_2$, $W_1$, $W_2$, $W_3$ and $W_4$ are as previously defined with respect to Formula (I).

In yet more preferred 1,3,4-oxadiazoles of the present invention, $R_1$ is a substituted
or unsubstituted aniline group (-NH-Aryl) and $R_2$ is a radical of formula -$NR_{7a}R_{7b}$.
Accordingly, yet more preferred 1,3,4-oxadiazoles of the present invention are those that
are encompassed by Formula (Ib')
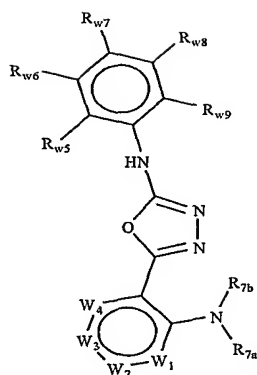
(Ib')

Yet more preferably, $W_1$ is nitrogen and $W_2$, $W_3$ and $W_4$ are each CH.

Methods of preparing 1,3,4-oxadiazoles are described in *Comprehensive*

*Heterocyclic Chemistry* Part 6, pp. 440-445 (Alan Katritzky and Charles Rees eds.,

Pergamon Press: Oxford 1984); *Heterocyclic Compounds* "Five- And Six-Membered

Compounds with Nitrogen And Oxygen" (Richard H. Wiley ed., John Wiley & Sons: New

York 1962), Katritzky, A.R.; Pozharskii, A.F. *Handbook of Heterocyclic Chemistry* 2nd

edition pp. 591-596 (Pergamon: NY 2000); Gilchrist, T.L. *Heterocyclic Chemistry* 3rd

edition, p. 336 (Longman Publ.: Singapore 1997); Joule, J.A. et al. *Heterocyclic*

*Chemistry* 3rd edition p.445 (Chapman & Hall: London 1995). These methods include

cyclization-dehydration of diacylhydrazines (RC(O)-NHNH-C(O)-R). Each of the

treatises referenced in this paragraph is hereby incorporated by reference in its entirety and,

in particular, for the discussion of methods of preparing 1,3,4-oxadiazoles contained on the

cited pages.

. In accordance with a particularly preferred process for preparing 1,3,4-oxadiazoles

of Formula (Ib'), a hydrazide of Formula (II) (wherein $R_2=NR_{7a}R_{7b}$), previously defined, is

contacted with an isothiocyanate of Formula (VI):
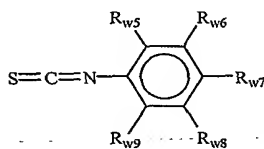


(VI)

to give an intermediate of Formula (VII).

29
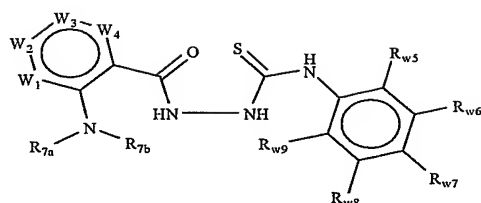
(VII)

This addition reaction is generally performed in an organic solvent, like dichloromethane, under neutral conditions and at ambient or elevated temperature at a concentration of about 1mM to about 2 M. The intermediate is then cyclized by treating it with a coupling agent like dicyclohexylcarbodiimide.

Isothiocyanate starting materials of Formula (VI) are either commercially available or can be conveniently prepared using well-establish techniques of functional group interconversion starting from the corresponding unsubstituted benzene derivative by electrophilic aromatic substituted with, e.g., ammonium thiocyanate; the corresponding nitro derivative by reaction with carbon disulfide; or the corresponding trialkylsilylamine, or amide by treatment with carbon disulfide and many other techniques described in *Comprehensive Organic Functional Group Transformations Vol. 5* pp. 1021-1045 (Katritzky, A.R. et al. editors, Elsevier Science Ltd: Oxford 1995) which is hereby incorporated by reference in its entirety and, in particular, for its description of methods of making isothiocyanates contained in the cited pages of the reference.

Oxazole VEGF Tyrosine Kinase Inhibitors

A third preferred class of 1,3-disubstituted five-membered ring heterocycles of Formula (I) are oxazoles. Oxazoles contain two double bonds, one oxygen atom and one nitrogen atom that is not adjacent to the oxygen atom in the five-membered heterocyclic ring. One preferred class of 1,3-disubstituted oxazoles are 2,5-disubstituted oxazoles (absolute numbering) encompassed by Formula (Ic):
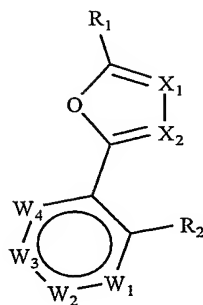
(Ic)

wherein either $X_1$ is nitrogen and $X_2$ is C-$R_3$ or $X_1$ is C-$R_3$ and $X_2$ is nitrogen, and $R_1$, $R_2$, $W_1$, $W_2$, $W_3$ and $W_4$ are as previously defined with respect to Formula (I).

In preferred 2,5-disubstituted oxazoles of the present invention, $R_1$ is optionally substituted phenyl, $W_1$, $W_2$, $W_3$ and $W_4$ are each CH and $R_2$ is -NH-$R_{7a}$. Especially preferred 2,5-disubstituted oxazoles are those encompassed by Formula (Ic'):
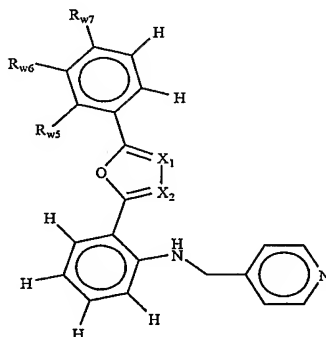


(Ic')

wherein $R_{w5}$, $R_{w6}$ and $R_{w7}$ are as previously defined with respect to Formula (I) and $X_1$ and $X_2$ are as previously defined with respect to Formula (Ic).

Methods of preparing oxazoles are described in *Comprehensive Heterocyclic Chemistry* Part 6, pp. 216-223 (Alan Katritzky and Charles Rees eds., Pergamon Press: Oxford 1984); *Heterocyclic Compounds* "Oxazoles Part A" Vol. 60 pp. 4-127 (David C. Palmer ed., John Wiley & Sons: New York 2003), Katritzky, A.R.; Pozharskii, A.F. *Handbook of Heterocyclic Chemistry* 2nd edition pp. 591-596 (Pergamon: NY 2000); Gilchrist, T.L. *Heterocyclic Chemistry* 3rd edition, pp. 320-322 (Longman Publ.: Singapore 1997); Joule, J.A. et al. *Heterocyclic Chemistry* 3rd edition pp.386-392

(Chapman & Hall: London 1995). These methods include cyclization-dehydration of α-acylaminocarbonyl compounds (R'C(O)C(R")-NH-C(O)-R"') known as the Robinson-Gabriel synthesis and the condensation of aldehyde cyanohydrins and aromatic aldehydes in dry ether in the presence of dry hydrochloric acid known as the Fischer Oxazole

5      synthesis. R. H. Wiley, *Chem. Rev.* **1945** *37,* 410; J. W. Cornforth, R. H. Cornforth, *J. Chem. Soc.* **1949**, 1028; J. W. Cornforth, *Heterocyclic Compounds* **1957**, *5*, 309; T. Onaka, *Tetrahedron Letters* **1971**, 4391. Each of the treatises and articles referenced in this paragraph is hereby incorporated by reference in its entirety and, in particular, for the discussion of methods of preparing oxazoles contained on the cited pages.

10

Imidazole VEGF Tyrosine Kinase Inhibitors

A fourth preferred class of 1,3-disubstituted five-membered ring heterocycles of Formula (I) are 2,4-disubstituted imidazoles. Imidazoles contain two double bonds and two non-adjacent nitrogen atoms in the five-membered heterocyclic ring. Accordingly,

15     one preferred class of 2,4-disubstituted imidazoles of the present invention are those that are encompassed by Formula (Id):



(Id)
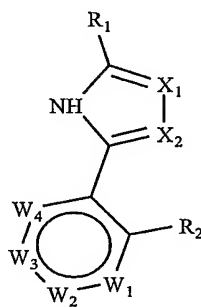
20     wherein either $X_1$ is nitrogen and $X_2$ is $-CR_3$ or $X_1$ is $-CR_3$ and $X_2$ is nitrogen and $R_1$, $R_2$, $W_1$, $W_2$, $W_3$ and $W_4$ are as defined with respect to Formula (I). In preferred 2,4-disubstituted imidazoles of the present invention, $X_1$ is $CR_3$ (more preferably CH or $CH_3$), and $X_2$ is nitrogen, $R_1$ is optionally substituted phenyl, $R_2$ is $-NH_2$, and $W_1$, $W_2$, $W_3$ and $W_4$ are each CH. Yet more preferred imidazoles of the present invention are those

25     encompassed by Formula (Id').

(Id')
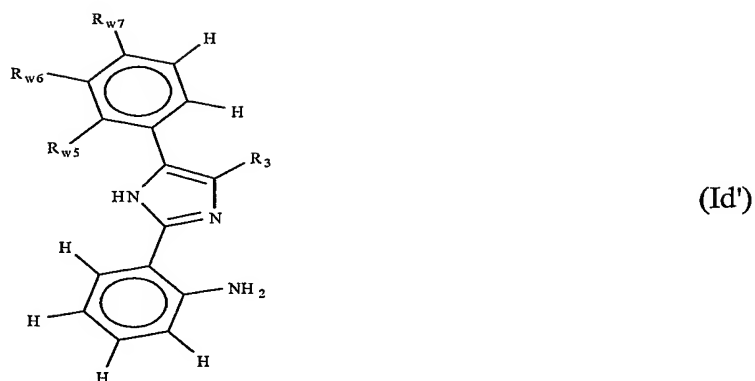
Methods of preparing imidazoles are described in *Comprehensive Heterocyclic Chemistry* Part 5, pp. 457-496 (Alan Katritzky and Charles Rees eds., Pergamon Press: Oxford 1984); *Heterocyclic Compounds* "Imidazole And Derivatives Part I" pp.33-43 (Klaus Hofmann ed., Interscience Publishers: New York 1953); Gilchrist, T.L. *Heterocyclic Chemistry* 3rd edition, pp. 299-300 (Longman Publ.: Singapore 1997); Joule, J.A. et al. *Heterocyclic Chemistry* 3rd edition pp. 384-387 (Chapman & Hall: London 1995). Each of the treatises referenced in this paragraph is hereby incorporated by reference in its entirety and, in particular, for the discussion of methods of preparing imidazoles contained on the cited pages.

In a preferred process, the imidazoles of this invention are prepared by contacting an amidine of Formula (V) with an α-halo carboxyl compound of Formula (VIII):



(VIII)

wherein substituent "hal" is bromine or iodine, or by contacting an amidine of Formula (III) with an α-halo ketone of Formula (IX):



(IX)

When $R_2$ is $NH_2$, $R_2$ is an interfering functionality. We overcame this problem by

using a 2-nitro analog of the (2-aminoaryl) α-halo ketone (IX) (NO$_2$ in place of R$_2$) and
then reducing the nitro group with palladium-on-carbon. Accordingly, imidazoles of
Formula (Id') may be prepared by a variation of the reaction expressed in Scheme III.

5                                    Scheme III



(IX')                    (III')                                                        (Id')
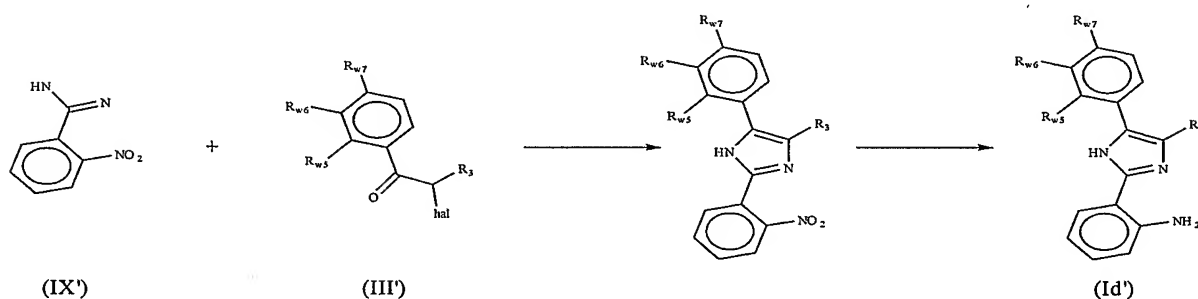
The cyclization reaction is generally performed in a polar aprotic solvent like DMF
or THF, under basic conditions at a concentration of about 1mM to about 2 M. If the
10   starting halide is a bromide, it can be activated by addition of sodium iodide to the reaction
mixture. In addition, the reaction mixture may be refluxed to accelerate the reaction. After
the cyclization, the nitro group is reduced using conditions well known in the art for
reducing aryl nitro groups to amines. Such conditions are summarized and citations to
primary references are given in Larock, R.C. *Comprehensive Organic Transformations*
15   *2nd ed.* pp. 823-827 (Wiley-VCH: New York 1999), which pages and the primary
references to which they refer are hereby incorporated by reference for their teachings how
to reduce nitroarenes to aminoarenes.
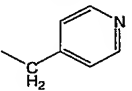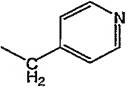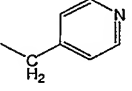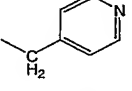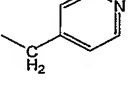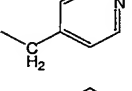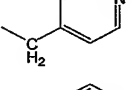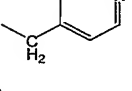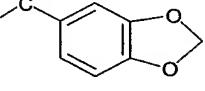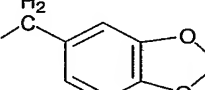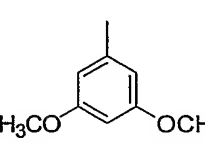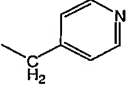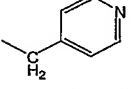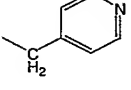
Specific representative compounds of the present invention are set forth in Tables
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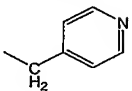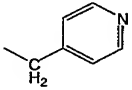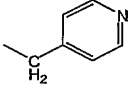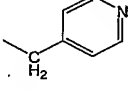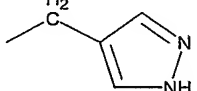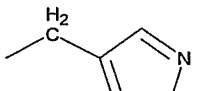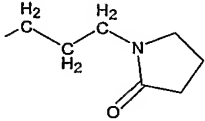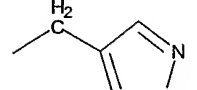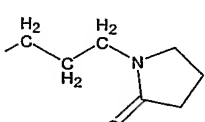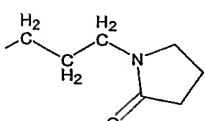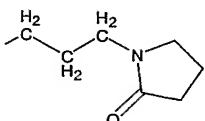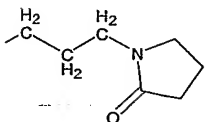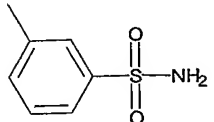
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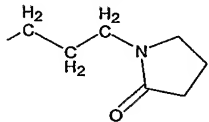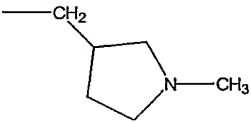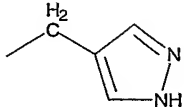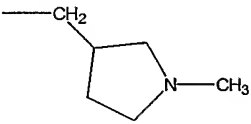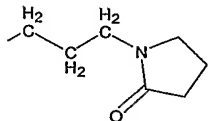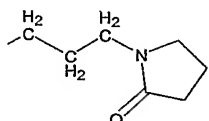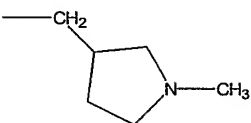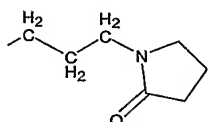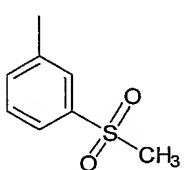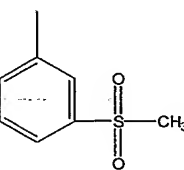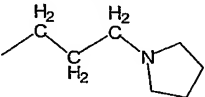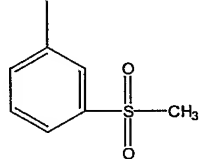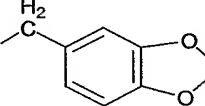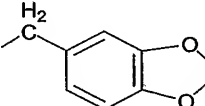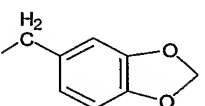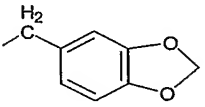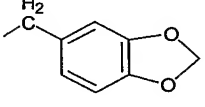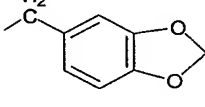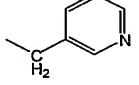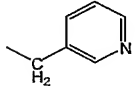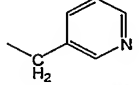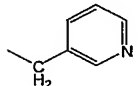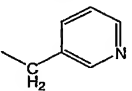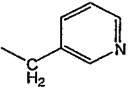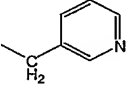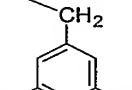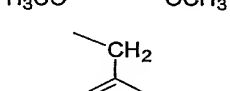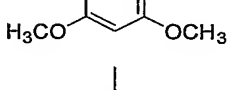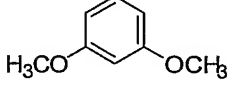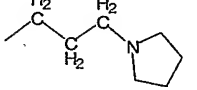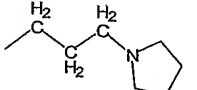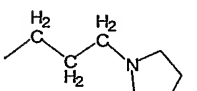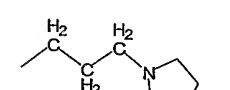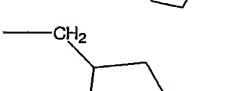
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Table 1
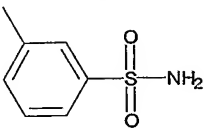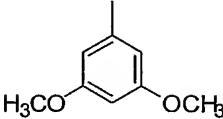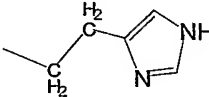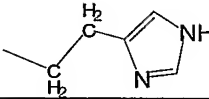


| | Cmpd. No. | W$_1$ | W$_6$ | R$_{w2}$ | R$_{w7}$ | R$_{w8}$ | R$_{7a}$ |
|---|---|---|---|---|---|---|---|
| 5 | 1 | CH | CH | H | H | H | pyridin-4-ylmethyl |
| | 2 | CH | CH | H | H | Br | pyridin-4-ylmethyl |
| | 3 | CH | CH | H | CF$_3$ | H | pyridin-4-ylmethyl |
| 10 | 4 | CH | CH | H | H | Cl | pyridin-4-ylmethyl |
| | 5 | CH | CH | H | C$_6$H$_5$ | H | pyridin-4-ylmethyl |
| | 6 | CH | CH | H | H | OCH$_2$C$_6$H$_5$ | pyridin-4-ylmethyl |
| | 7 | CH | CH | H | OCH$_2$C$_6$H$_5$ | H | pyridin-4-ylmethyl |
| | 8 | CH | CH | Cl | H | CF$_3$ | pyridin-4-ylmethyl |
| 15 | 9 | N | CH | H | H | CF$_3$ | pyridin-4-ylmethyl |
| | 10 | CH | CH | H | H | OC$_6$H$_5$ | pyridin-4-ylmethyl |

| Cmpd. No. | W$_1$ | W$_6$ | R$_{w2}$ | R$_{w7}$ | R$_{w8}$ | R$_{7a}$ |
|---|---|---|---|---|---|---|
| 11 | CH | CH | H | OC$_6$H$_5$ | H |  |
| 12 | CH | CH | H | -CCH | H |  |
| 13 | CH | CH | H | H | C$_6$H$_5$ |  |
| 14 | CH | CH | H | H | trans-CH=CH-C$_6$H$_5$ |  |
| 15 | CH | CH | H | H | (CH$_2$)$_3$N(CH$_3$)$_2$ |  |
| 16 | CH | CH | H | (CH$_2$)$_3$N(CH$_3$)$_2$ | H |  |
| 17 | CH | CH | H | H | CF$_3$ |  |
| 18 | CH | CH | H | H | CF$_3$ |  |
| 19 | N | CH | H | SO$_2$CH$_3$ | H |  |
| 20 | N | CH | H | OCH$_3$ | OCH$_3$ |  |
| 21 | N | CH | H | H | OCH$_3$ |  |
| 22 | CH | CH | H | OCH$_3$ | OCH$_3$ |  |
| 23 | CH | CH | H | -O-CH$_2$-O- | |  |
| 24 | CH | CH | H | F | Cl |  |

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| Cmpd. No. | $W_1$ | $W_6$ | $R_{w2}$ | $R_{w7}$ | $R_{w8}$ | $R_{7a}$ |
|-----------|-------|-------|----------|----------|----------|----------|
| 25 | CH | CH | H | H | F |  |
| 26 | CH | CH | H | $CF_3$ | H |  |
| 27 | CH | $COCH_3$ | H | H | $OCH_3$ |  |
| 28 | CH | CH | H | $SO_2CH_3$ | H |  |
| 29 | CH | N | H | H | H |  |
| 30 | CH | CH | H | H | $CF_3$ |  |
| 31 | N | CH | H | $OCH_3$ | H |  |
| 32 | CH | CH | H | $OCH_3$ | H |  |
| 33 | N | CH | H | $SO_2CH_3$ | H |  |
| 34 | N | CH | H | $-O-CH_2-O-$ | |  |
| 35 | N | CH | H | H | $CF_3$ |  |
| 36 | N | CH | H | H | $OCH_3$ |  |
| 37 | N | CH | H | $-O-CH_2-O-$ | |  |

| Cmpd. No. | $W_1$ | $W_6$ | $R_{w2}$ | $R_{w7}$ | $R_{w8}$ | $R_{7a}$ |
|---|---|---|---|---|---|---|
| 38 | N | CH | H | $OCH_3$ | $OCH_3$ | (2-oxopyrrolidin-1-yl)propyl group |
| 39 | N | CH | H | H | $OCH_3$ | (1-methylpyrrolidin-3-yl)methyl group |
| 40 | CH | CH | H | -O-CH$_2$-O- | | (1H-pyrazol-4-yl)methyl group |
| 41 | N | N | H | H | H | (1-methylpyrrolidin-3-yl)methyl group |
| 42 | N | CH | H | -O-CH$_2$-O- | | (2-oxopyrrolidin-1-yl)propyl group |
| 43 | N | N | H | H | H | (2-oxopyrrolidin-1-yl)propyl group |
| 44 | N | CH | H | H | $CF_3$ | (1-methylpyrrolidin-3-yl)methyl group |
| 45 | N | CH | H | H | $CF_3$ | (2-oxopyrrolidin-1-yl)propyl group |
| 46 | N | CH | H | -O-CH$_2$-O- | | (3-(methylsulfonyl)phenyl)methyl group |
| 47 | N | CH | H | H | $CF_3$ | (3-(methylsulfonyl)phenyl)methyl group |

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38

| Cmpd. No. | $W_1$ | $W_6$ | $R_{w2}$ | $R_{w7}$ | $R_{w8}$ | $R_{7a}$ |
|---|---|---|---|---|---|---|
| 48 | N | N | H | H | H |  |
| 49 | N | CH | H | H | $OCH_3$ |  |
| 50 | N | CH | H | H | $OCH_3$ |  |
| 51 | N | $COCH_3$ | H | H | $OCH_3$ |  |
| 52 | N | CH | H | F | Cl |  |
| 53 | N | CH | H | H | F |  |
| 54 | N | CH | H | H | $CF_3$ |  |
| 55 | N | CH | H | $CF_3$ | H |  |
| 56 | N | CH | H | H | $OCH_3$ |  |
| 57 | N | CH | H | F | Cl |  |
| 58 | N | CH | H | H | F |  |
| 59 | N | CH | H | $CF_3$ | H |  |

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| Cmpd. No. | $W_1$ | $W_6$ | $R_{w2}$ | $R_{w7}$ | $R_{w8}$ | $R_{7a}$ |
|---|---|---|---|---|---|---|
| 60 | N | $COCH_3$ | H | H | $OCH_3$ | (pyridin-3-yl)CH₂– |
| 61 | N | CH | H | $OCH_3$ | $OCH_3$ | (pyridin-3-yl)CH₂– |
| 62 | N | CH | H | $SO_2CH_3$ | H | (pyridin-3-yl)CH₂– |
| 63 | N | CH | H | $OCH_3$ | $OCH_3$ | 3,5-di($H_3CO$)benzyl ($CH_2$) |
| 64 | N | CH | H | $SO_2CH_3$ | H | 3,5-di($H_3CO$)benzyl ($CH_2$) |
| 65 | N | CH | H | H | $OCH_3$ | 3,5-di($H_3CO$)phenyl, CH₃ |
| 66 | N | CH | H | H | $CF_3$ | –CH₂–CH₂–CH₂–pyrrolidin-1-yl |
| 67 | N | CH | H | H | $OCH_3$ | –CH₂–CH₂–CH₂–pyrrolidin-1-yl |
| 68 | N | CH | H | $-O-CH_2-O-$ | | –CH₂–CH₂–CH₂–pyrrolidin-1-yl |
| 69 | N | $COCH_3$ | H | H | $OCH_3$ | –CH₂–CH₂–CH₂–pyrrolidin-1-yl |
| 70 | N | CH | H | H | $OCH_3$ | (1-methylpyrrolidin-3-yl)–CH₂– |
| 71 | N | CH | H | H | $OCH_3$ | (3-methyl-benzenesulfonamide)– |

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| Cmpd. No. | $W_1$ | $W_6$ | $R_{w2}$ | $R_{w7}$ | $R_{w8}$ | $R_{7a}$ |
|---|---|---|---|---|---|---|
| 72 | N | CH | H | H | $CF_3$ | 3-methylbenzenesulfonamide |
| 73 | N | N | H | H | H | 3,5-dimethoxyphenyl (methyl) |
| 74 | N | CH | H | -O-CH$_2$-O- | | (imidazol-4-yl)propyl |
| 75 | N | CH | H | H | $OCH_3$ | (imidazol-4-yl)propyl |

Table 2



| Compound No. | $X_1$ | $X_2$ |
|---|---|---|
| 76 | N | N |
| 77 | N | C |
| 78 | C | N |
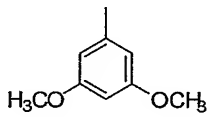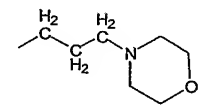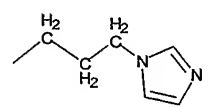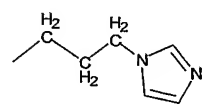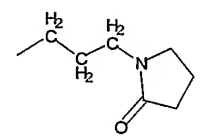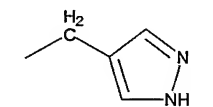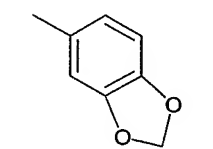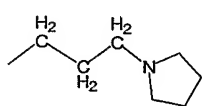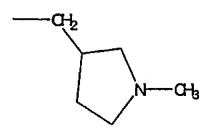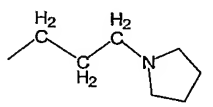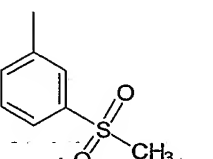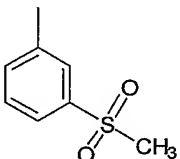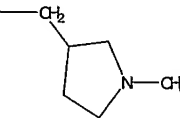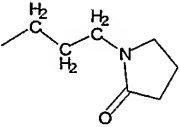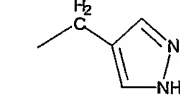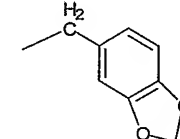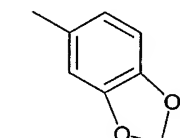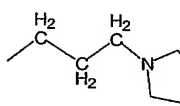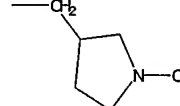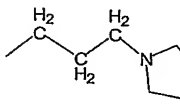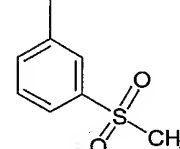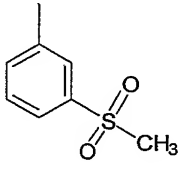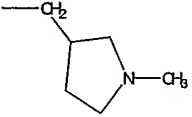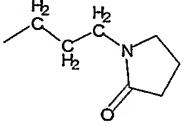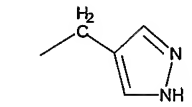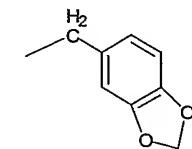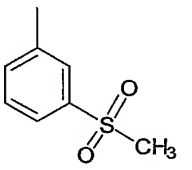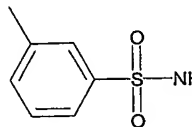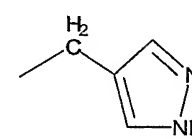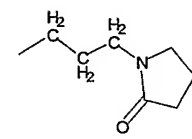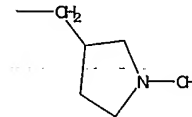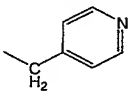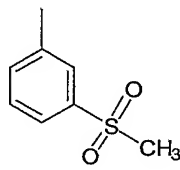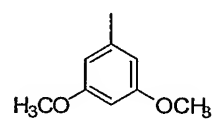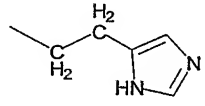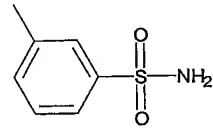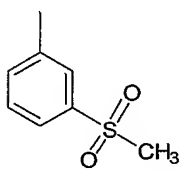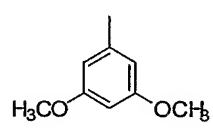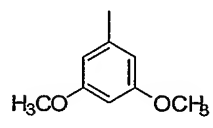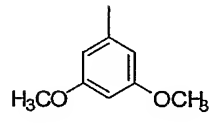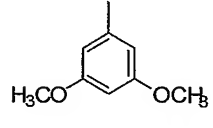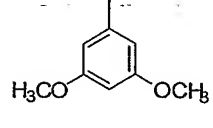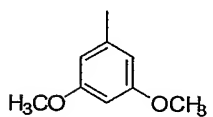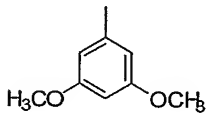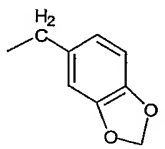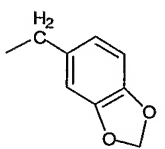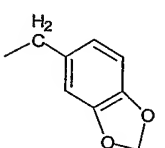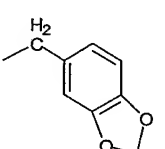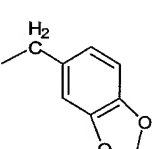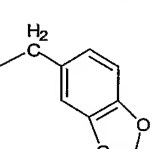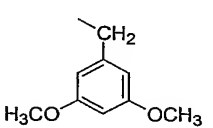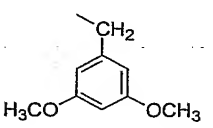
## Table 3

$R_{w7}$, $R_{w8}$, $R_{w6}$, $R_{w9}$, $R_{w5}$—Z connected to a triazole ($X_3$, N, N) linked to a pyridine ring ($W_1$) bearing $N(R_{7a})(R_{7b})$ and H substituents.
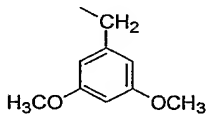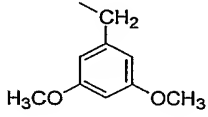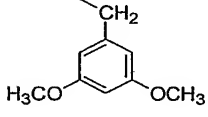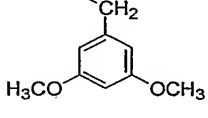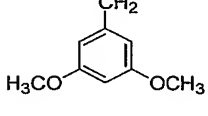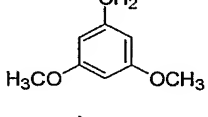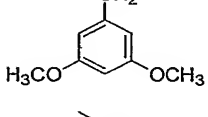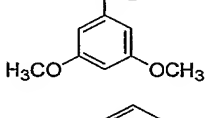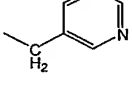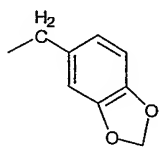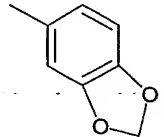
| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 79 | N | NH | NH | H | -O-CH₂-O- | | H | H | 3,5-dimethoxybenzyl (CH₂-C₆H₃(OCH₃)₂) | H |
| 80 | N | NH | NH | H | -O-CH₂-O- | | H | H | pyridin-3-ylmethyl (CH₂-pyridine) | H |
| 81 | N | NH | NH | H | -O-CH₂-O- | | H | H | pyridin-4-ylmethyl (CH₂-pyridine) | H |
| 82 | N | NH | CH₂ | H | OCH₃ | H | H | H | pyridin-4-ylmethyl (CH₂-pyridine) | H |
| 83 | N | NH | NH | H | OCH₃ | H | H | H | 3-(2-oxopyrrolidin-1-yl)propyl | H |
| 84 | N | O | NH | H | OCH₃ | OCH₃ | H | H | 3-(2-oxopyrrolidin-1-yl)propyl | H |
| 85 | N | O | NH | H | -O-CH₂-O- | | H | H | 3-(2-oxopyrrolidin-1-yl)propyl | H |
| 86 | N | NH | CH₂O | H | H | F | H | H | pyridin-4-ylmethyl (CH₂-pyridine) | H |

| Cmpd. No. | W$_1$ | X$_3$ | Z | R$_{w5}$ | R$_{w6}$ | R$_{w7}$ | R$_{w8}$ | R$_{w9}$ | R$_{7a}$ | R$_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 87 | N | NH | CH2 | H | OCH$_3$ | H | H | H | (3,5-dimethoxyphenyl)methyl | H |
| 88 | N | NH | NH | H | OCH$_3$ | H | H | H | 3-(morpholin-4-yl)propyl | H |
| 89 | N | NH | NH | H | H | N(CH$_3$)$_2$ | H | H | 3-(imidazol-1-yl)propyl | H |
| 90 | N | NH | NH | H | OCH$_3$ | H | H | H | 3-(imidazol-1-yl)propyl | H |
| 91 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | 3-(2-oxopyrrolidin-1-yl)propyl | H |
| 92 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | (pyrazol-4-yl)methyl | H |
| 93 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | (methylbenzodioxol)methyl | H |
| 94 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | 3-(pyrrolidin-1-yl)propyl | H |
| 95 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | (1-methylpyrrolidin-3-yl)methyl | H |
| 96 | N | NH | NH | H | OCH$_3$ | H | H | H | 3-(pyrrolidin-1-yl)propyl | H |
| 97 | N | NH | NH | H | OCH$_3$ | H | H | H | (3-methylsulfonylphenyl) | H |

| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 98 | N | NH | NH | H | -O-CH₂-O- | | H | H |  | H |
| 99 | N | NH | NH | H | OCH₃ | H | H | H |  | H |
| 100 | N | NH | CH₂ | H | OCH₃ | H | H | H |  | H |
| 101 | N | NH | CH₂ | H | OCH₃ | H | H | H |  | H |
| 102 | N | NH | NH | H | -O-CH₂-O- | | H | H |  | H |
| 93 | N | NH | NH | H | -O-CH₂-O- | | H | H |  | H |
| 94 | N | NH | NH | H | -O-CH₂-O- | | H | H |  | H |
| 95 | N | NH | NH | H | -O-CH₂-O- | | H | H |  | H |
| 96 | N | NH | NH | H | OCH₃ | H | H | H |  | H |
| 97 | N | NH | NH | H | OCH₃ | H | H | H |  | H |
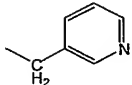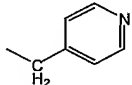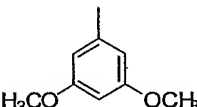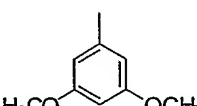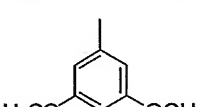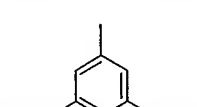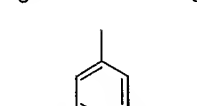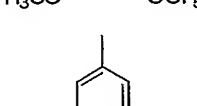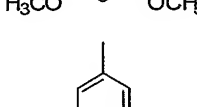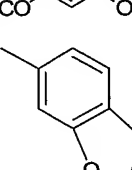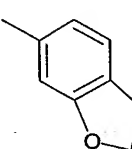
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| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 98 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | | H |
| 99 | N | NH | NH | H | OCH$_3$ | H | H | H | | H |
| 100 | N | NH | CH$_2$ | H | OCH$_3$ | H | H | H | | H |
| 101 | N | NH | CH$_2$ | H | OCH$_3$ | H | H | H | | H |
| 102 | N | NH | NH | H | -O-CH$_2$-O- | | H | H | | H |
| 103 | N | O | NH | H | -O-CH$_2$CH$_2$-O- | | H | H | | H |
| 104 | N | O | NH | H | -O-CH$_2$CH$_2$-O- | | H | H | | H |
| 105 | N | O | NH | H | -O-CH$_2$CH$_2$-O- | | H | H | | H |
| 106 | N | O | NH | H | -O-CH$_2$CH$_2$-O- | | H | H | | H |
| 107 | N | O | NH | H | -O-CH$_2$CH$_2$-O- | | H | H | | H |

| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 108 | N | O | NH | H | $-O-CH_2CH_2-O-$ | | H | H | 1-(pyridin-4-yl)ethyl | H |
| 109 | N | O | NH | H | $-O-CH_2-O-$ | | H | H | 3-(methylsulfonyl)benzyl | H |
| 110 | N | O | NH | H | $-O-CH_2CH_2-O-$ | | H | H | 3,5-dimethoxybenzyl | H |
| 111 | N | O | NH | H | $-O-CH_2CH_2-O-$ | | H | H | 2-(1H-imidazol-4-yl)ethyl (propyl-imidazole) | H |
| 112 | N | O | NH | H | $-O-CH_2-O-$ | | H | H | 3-sulfamoylbenzyl | H |
| 113 | N | O | NH | H | H | $SO_2NH_2$ | H | H | 3-(methylsulfonyl)benzyl | H |
| 114 | N | O | NH | H | H | $OCF_3$ | H | H | 3,5-dimethoxybenzyl | H |
| 115 | N | O | NH | H | F | H | F | H | 3,5-dimethoxybenzyl | H |
| 116 | N | O | NH | H | $OCF_3$ | H | H | H | 3,5-dimethoxybenzyl | H |
| 117 | N | O | NH | H | $OCH_2$ $C_6H_5$ | H | H | H | 3,5-dimethoxybenzyl | H |
| 118 | N | O | NH | H | $-O-CH_2-O-$ | | H | H | 3,5-dimethoxybenzyl | H |

| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 119 | N | O | NH | H | $OCH_3$ | $OCH_3$ | H | H | 3,5-dimethoxyphenyl ($H_3CO$—ring—$OCH_3$) | H |
| 120 | N | O | NH | H | H | $OC_6H_5$ | H | H | 3,5-dimethoxyphenyl ($H_3CO$—ring—$OCH_3$) | H |
| 121 | N | O | NH | H | H | $OCF_3$ | H | H | benzo[1,3]dioxol-5-ylmethyl ($H_2C$—) | H |
| 122 | N | O | NH | H | $CF_3$ | H | H | H | benzo[1,3]dioxol-5-ylmethyl ($H_2C$—) | H |
| 123 | N | O | NH | H | $OCH_2$ $C_6H_5$ | H | H | H | benzo[1,3]dioxol-5-ylmethyl ($H_2C$—) | H |
| 124 | N | O | NH | H | H | $OC_6H_5$ | H | H | benzo[1,3]dioxol-5-ylmethyl ($H_2C$—) | H |
| 125 | N | O | NH | H | $OCH_3$ | $OCH_3$ | H | H | benzo[1,3]dioxol-5-ylmethyl ($H_2C$—) | H |
| 126 | N | O | NH | H | $-O-CH_2-O-$ | | H | H | benzo[1,3]dioxol-5-ylmethyl ($H_2C$—) | H |
| 127 | N | O | NH | H | H | $OCF_3$ | H | H | 3,5-dimethoxybenzyl ($—CH_2$; $H_3CO$—ring—$OCH_3$) | H |
| 128 | N | O | NH | H | $CF_3$ | H | H | H | 3,5-dimethoxybenzyl ($—CH_2$; $H_3CO$—ring—$OCH_3$) | H |
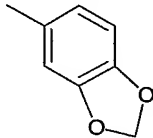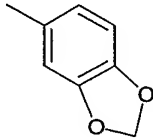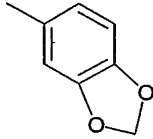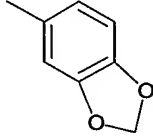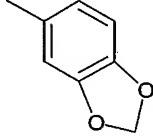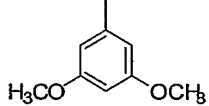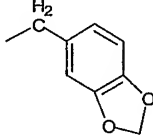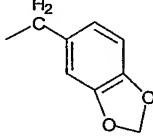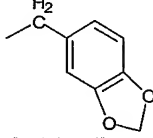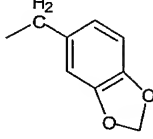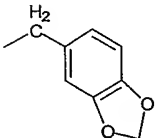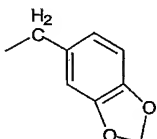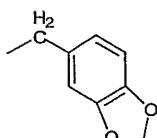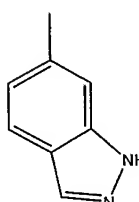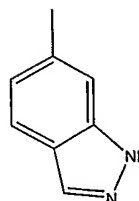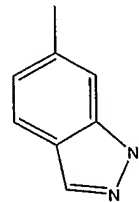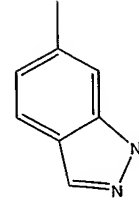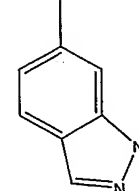
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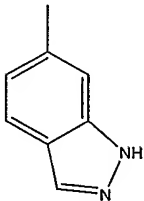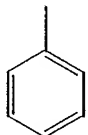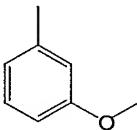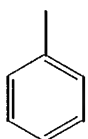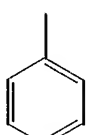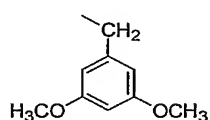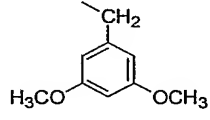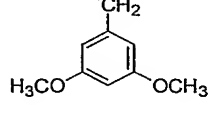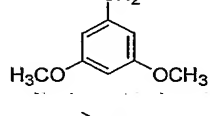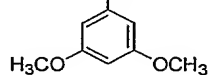
| Cmpd. No. | W$_1$ | X$_3$ | Z | R$_{w5}$ | R$_{w6}$ | R$_{w7}$ | R$_{w8}$ | R$_{w9}$ | R$_{7a}$ | R$_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 129 | N | O | NH | H | H | OC$_6$H$_5$ | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 130 | N | O | NH | H | OCH$_2$C$_6$H$_5$ | H | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 131 | N | O | NH | H | -O-CH$_2$-O- | | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 132 | N | O | NH | H | OCH$_3$ | OCH$_3$ | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 133 | N | O | NH | H | F | H | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 134 | N | O | NH | H | H | CF$_3$ | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 135 | N | O | NH | H | -CH$_2$CH$_2$CH$_2$- | | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 136 | N | O | NH | H | OCH$_3$ | H | H | H | 3,5-dimethoxybenzyl (CH$_2$) | H |
| 137 | N | O | NH | H | OCH$_3$ | H | H | H | pyridin-3-ylmethyl (CH$_2$) | H |
| 138 | N | O | NH | H | OCH$_3$ | H | H | H | benzo[1,3]dioxol-5-ylmethyl (CH$_2$) | H |
| 139 | N | O | NH | H | OCH$_3$ | H | OCH$_3$ | H | benzo[1,3]dioxol-5-yl | H |

| Cmpd. No. | W₁ | X₃ | Z | Rw5 | Rw6 | Rw7 | Rw8 | Rw9 | R7a | R7b |
|---|---|---|---|---|---|---|---|---|---|---|
| 140 | N | O | NH | H | OCH₃ | H | OCH₃ | H | (3,5-dimethoxyphenyl, H₃CO / OCH₃) | H |
| 141 | N | O | NH | H | OCH₃ | H | H | H | (methylenedioxyphenyl, O-CH₂-O) | H |
| 142 | N | O | NH | H | OCH₃ | H | H | H | (3,5-dimethoxybenzyl, CH₂; H₃CO / OCH₃) | H |
| 143 | N | O | NH | H | OCH₃ | H | H | H | (pyridinyl-CH₂, N) | H |
| 144 | N | O | NH | H | OCH₃ | H | OCH₃ | H | (pyridinyl-CH₂, N) | H |
| 145 | N | O | NH | H | OCH₃ | H | OCH₃ | H | (3,5-dimethoxybenzyl, CH₂; H₃CO / OCH₃) | H |
| 146 | N | O | NH | H | OCH₃ | H | OCH₃ | H | (methylenedioxyphenyl-CH₂, O-CH₂-O) | H |
| 147 | N | O | NH | H | H | CF₃ | H | H | (pyridinyl-CH₂, N) | H |
| 148 | N | O | NH | H | -O-CH₂-O- | | H | H | (pyridinyl-CH₂, N) | H |
| 149 | N | O | NH | H | H | OC₆H₅ | H | H | (pyridinyl-CH₂, N) | H |
| 150 | N | O | NH | H | OCH₃ | OCH₃ | H | H | (pyridinyl-CH₂, N) | H |
| 151 | N | NH | CH₂O | H | H | F | H | H | (methylenedioxyphenyl-CH₂, O-CH₂-O) | H |

| Cmpd. No. | W₁ | X₃ | Z | R_{w5} | R_{w6} | R_{w7} | R_{w8} | R_{w9} | R_{7a} | R_{7b} |
|---|---|---|---|---|---|---|---|---|---|---|
| 152 | N | NH | CH₂O | H | H | F | H | H | (3-pyridyl)CH₂– | H |
| 153 | N | NH | CH₂O | H | H | F | H | H | (4-pyridyl)CH₂– | H |
| 154 | N | NH | NH | H | OCH₃ | H | OCH₃ | H | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 155 | N | NH | NH | H | OCH₃ | H | H | H | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 156 | N | NH | NH | H | H | OCH₃ | H | H | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 157 | N | NH | NH | H | H | CN | H | H | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 158 | N | NH | NH | H | H | H | H | H | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 159 | N | NH | NH | OCH₃ | H | H | H | OCH₃ | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 160 | N | NH | NH | H | H | N(CH₃)₂ | H | H | 3,5-dimethoxyphenyl (H₃CO / OCH₃) | H |
| 161 | N | NH | NH | H | OCH₃ | H | H | H | benzo[1,3]dioxol-5-yl (methylenedioxyphenyl) | H |
| 162 | N | NH | NH | H | H | OCH₃ | H | H | benzo[1,3]dioxol-5-yl (methylenedioxyphenyl) | H |
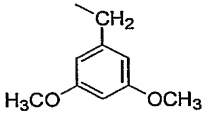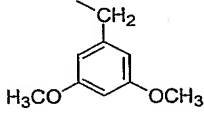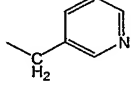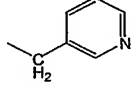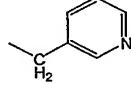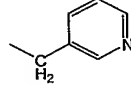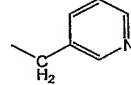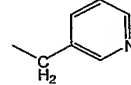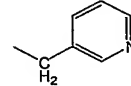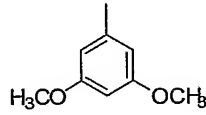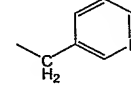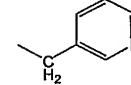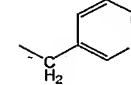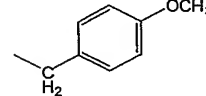
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| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 163 | N | NH | NH | H | H | CN | H | H | methyl-benzo[1,3]dioxole | H |
| 164 | N | NH | NH | $OCH_3$ | H | H | H | $OCH_3$ | methyl-benzo[1,3]dioxole | H |
| 165 | N | NH | NH | $OCH_3$ | H | $OCH_3$ | H | H | methyl-benzo[1,3]dioxole | H |
| 166 | N | NH | NH | H | $OCH_3$ | H | $OCH_3$ | H | methyl-benzo[1,3]dioxole | H |
| 167 | N | NH | NH | H | H | $N(CH_3)_2$ | H | H | methyl-benzo[1,3]dioxole | H |
| 168 | N | NH | NH | $OCH_3$ | H | $OCH_3$ | H | H | 3,5-dimethoxy-methylbenzene ($H_3CO$—, —$OCH_3$) | H |
| 169 | N | NH | NH | H | $OCH_3$ | H | H | H | $CH_2$-benzo[1,3]dioxole | H |
| 170 | N | NH | NH | H | H | $OCH_3$ | H | H | $CH_2$-benzo[1,3]dioxole | H |
| 171 | N | NH | NH | H | H | CN | H | H | $CH_2$-benzo[1,3]dioxole | H |
| 172 | N | NH | NH | $OCH_3$ | H | H | H | $OCH_3$ | $CH_2$-benzo[1,3]dioxole | H |

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| Cmpd. No. | W₁ | X₃ | Z | R_w5 | R_w6 | R_w7 | R_w8 | R_w9 | R_7a | R_7b |
|---|---|---|---|---|---|---|---|---|---|---|
| 173 | N | NH | NH | H | H | N(CH₃)₂ | H | H |  | H |
| 174 | N | NH | NH | H | OCH₃ | H | OCH₃ | H |  | H |
| 175 | N | NH | NH | OCH₃ | H | OCH₃ | H | H |  | H |
| 176 | N | NH | NH | H | OCH₃ | H | H | H |  | H |
| 177 | N | NH | NH | H | H | OCH₃ | H | H |  | H |
| 178 | N | NH | NH | H | H | CN | H | H |  | H |
| 179 | N | NH | NH | OCH₃ | H | H | H | OCH₃ |  | H |
| 180 | N | NH | NH | H | H | N(CH₃)₂ | H | H |  | H |

| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 181 | N | NH | NH | $OCH_3$ | H | $OCH_3$ | H | H | (6-indazolyl) | H |
| 182 | N | NH | NH | H | $OCH_3$ | H | $OCH_3$ | H | (phenyl) | H |
| 183 | N | NH | NH | H | $OCH_3$ | H | H | H | (3-methoxyphenyl) | H |
| 184 | N | NH | NH | H | H | H | H | H | (phenyl) | H |
| 185 | N | NH | NH | H | $OCH_3$ | H | H | H | (phenyl) | H |
| 186 | N | NH | NH | H | $OCH_3$ | H | $OCH_3$ | H | (3,5-dimethoxybenzyl) | H |
| 187 | N | NH | NH | H | $OCH_3$ | H | H | H | (3,5-dimethoxybenzyl) | H |
| 188 | N | NH | NH | H | H | $OCH_3$ | H | H | (3,5-dimethoxybenzyl) | H |
| 189 | N | NH | NH | H | $OCH_3$ | H | $OCH_3$ | H | (3,5-dimethoxybenzyl) | H |
| 190 | N | NH | NH | H | H | CN | H | H | (3,5-dimethoxybenzyl) | H |

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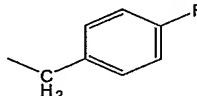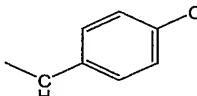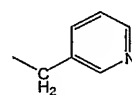
| Cmpd. No. | W$_1$ | X$_3$ | Z | R$_{w5}$ | R$_{w6}$ | R$_{w7}$ | R$_{w8}$ | R$_{w9}$ | R$_{7a}$ | R$_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 191 | N | NH | NH | OCH$_3$ | H | OCH$_3$ | H | H | 3,5-dimethoxybenzyl (–CH$_2$–C$_6$H$_3$(OCH$_3$)$_2$) | H |
| 192 | N | NH | NH | H | H | N(CH$_3$)$_2$ | H | H | 3,5-dimethoxybenzyl (–CH$_2$–C$_6$H$_3$(OCH$_3$)$_2$) | H |
| 193 | N | NH | NH | H | OCH$_3$ | H | OCH$_3$ | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 194 | N | NH | NH | H | OCH$_3$ | H | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 195 | N | NH | NH | H | H | OCH$_3$ | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 196 | N | NH | NH | OCH$_3$ | H | OCH$_3$ | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 197 | N | NH | NH | OCH$_3$ | H | H | H | OCH$_3$ | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 198 | N | NH | NH | H | H | CN | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 199 | N | NH | NH | H | H | N(CH$_3$)$_2$ | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 200 | N | O | NH | H | OCH$_3$ | H | H | H | 3,5-dimethoxy-benzyl (–CH$_2$–C$_6$H$_3$(OCH$_3$)$_2$) | H |
| 201 | CH | NH | NH | H | OCH$_3$ | H | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 202 | CH | NH | NH | H | H | OCH$_3$ | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 203 | CH | NH | NH | H | H | CN | H | H | pyridin-3-ylmethyl (–CH$_2$–pyridine) | H |
| 204 | CH | O | NH | H | OCH$_3$ | H | H | H | 4-methoxybenzyl (–CH$_2$–C$_6$H$_4$–OCH$_3$) | H |

| Cmpd. No. | $W_1$ | $X_3$ | Z | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{w8}$ | $R_{w9}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 205 | CH | O | NH | H | $OCH_3$ | H | H | H | $-CH_2-$(4-fluorophenyl) | H |
| 206 | CH | O | NH | H | $OCH_3$ | H | H | H | $-CH_2-$(4-chlorophenyl) | H |
| 207 | CH | O | NH | H | $OCH_3$ | H | $OCH_3$ | H | $-CH_2-$(pyridin-3-yl) | H |
| 208 | N | NH | NH | H | $-O-CH_2-O-$ | | H | H | $-CH_2CH_2N(CH_3)CH_2CH_2-$ | |
| 209 | N | NH | $CH_2$ | H | $OCH_3$ | H | H | H | $-CH_2CH_2N(CH_3)CH_2CH_2-$ | |
| 210 | N | O | NH | H | $-O-CH_2CH_2-O-$ | | H | H | $-CH_2CH_2N(CH_3)CH_2CH_2-$ | |
| 211 | CH | O | NH | H | $OCH_3$ | H | H | H | H | H |
| 212 | CH | NH | NH | $OCH_3$ | $OCH_3$ | H | H | H | H | H |
| 213 | CH | NH | NH | H | H | $N(CH_3)_2$ | H | H | H | H |

## Table 4
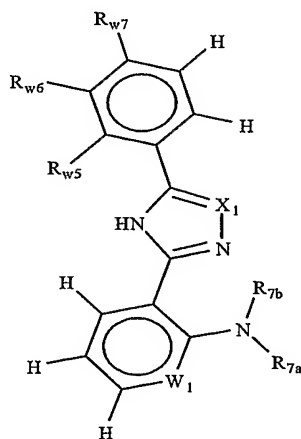


| Cmpd. No. | $X_1$ | $W_1$ | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|
| 214 | N | N | H | $OCH_3$ | H | $-CH_2CH_2N(CH_3)CH_2CH_2-$ | |
| 215 | N | N | H | $CF_3$ | H | $-CH_2CH_2N(CH_3)CH_2CH_2-$ | |
| 216 | N | N | H | $-O-CH_2-O-$ | | $-CH_2CH_2N(CH_3)CH_2CH_2-$ | |
| 217 | CH | CH | H | $CF_3$ | H | H | H |

55

| Cmpd. No. | $X_1$ | $W_1$ | $R_{w5}$ | $R_{w6}$ | $R_{w7}$ | $R_{7a}$ | $R_{7b}$ |
|---|---|---|---|---|---|---|---|
| 218 | N | CH | H | $OCF_3$ | H | H | H |
| 219 | N | CH | Cl | H | H | H | H |
| 220 | N | CH | H | $OCH_3$ | H | H | H |
| 221 | N | CH | H | H | Br | H | H |
| 222 | N | CH | H | Br | H | H | H |
| 223 | $C-CH_3$ | CH | H | $CF_3$ | H | H | H |
| 224 | N | CH | H | H | $OCF_3$ | H | H |
| 225 | N | CH | H | H | $CF_3$ | H | H |
| 226 | N | CH | H | H | $CF_3$ | H | H |

## Pharmaceutical Compositions and Dosage Forms Useful in The Treatment Of Angiogenic Dependent Diseases

Other aspects of the present invention are pharmaceutical compositions and dosage forms containing at least one compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or pro-drug thereof, in combination with a pharmaceutically acceptable carrier.

As used herein, the terms "pharmaceutically acceptable salts" and "hydrates" refer to those salts and hydrated forms of the compound that would favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which those skilled in the art may take into account in the selection include the cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug.

When a compound of the present invention is present as a salt or hydrate that is not pharmaceutically acceptable, that compound can be converted in certain circumstances to a salt or hydrate form that is pharmaceutically acceptable in accordance with the present invention.

5          When the compound is negatively charged, it is balanced by a counterion, such as, an alkali metal cation such as sodium or potassium. Other suitable counterions include calcium, magnesium, zinc, ammonium, or alkylammonium cations, such as tetramethylammonium, tetrabutylammonium, choline, triethylhydroammonium, meglumine, triethanol-hydroammonium, and the like. An appropriate number of

10        counterions are associated with the molecule to maintain overall charge neutrality. Likewise, when the compound is positively charged, e.g., protonated, an appropriate number of negatively charged counterions are present to maintain overall charge neutrality. These pharmaceutically acceptable salts are within the scope of the present invention.

           Pharmaceutically acceptable salts of bases may be prepared by the addition of an

15        appropriate acid. Thus, the compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. Examples include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride,

20        hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, pamoate, pectinate, persulfate, 3-phenylpropionate, pivalate, propionate, succinate, tartrate and undecanoate.

           If the compound has an acidic proton, a salt may be formed by the addition of base to form a pharmaceutically acceptable base addition salt. Base salts include ammonium

25        salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

           The basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides;

30        dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such

as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like
benzyl and phenethyl bromides and others.

5          The compounds of the present invention may be employed in solid or liquid form
including, for example, amorphous powder or crystalline form, in solution or in
suspension. They may be administered in numerous different ways, such as orally,
parenterally (intravenously or intramuscularly), topically, transdermally or by inhalation.
The choice of carrier and the content of active compound in the carrier are generally
determined in accordance with the solubility and chemical properties of the desired
product, the particular mode of administration and well established pharmaceutical
10         practice. The carrier may be either solid or liquid.

           Examples of liquid carriers include syrup, peanut oil, olive oil, water and the like.
For parenteral administration, emulsions, suspensions or solutions of the compounds
according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive
oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic
15         esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically
acceptable salts, are used. Injectable forms must be fluid to the extent they can be easily
syringed, and proper fluidity can be maintained, for example, by the use of a coating such
as lecithin, by the maintenance of the required particle size in the case of dispersion and by
the use of surfactants. Prolonged absorption of the injectable compositions can be brought
20         about by use of agents delaying absorption, for example, aluminum monostearate and
gelatin.

           The active compound may be orally administered with an ingestible solid carrier.
Compounds of the invention may be enclosed in hard or soft shell gelatin capsules, or
compressed into tablets, or incorporated directly with the food of the diet, or may be used
25         in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions,
syrups, wafers, and the like. Examples of oral solid dosage forms include tablets, capsules,
troches, lozenges and the like. Examples of oral liquid dosage forms include solutions,
suspensions, syrups, emulsions, soft gelatin capsules and the like. Carriers for oral use
(solid or liquid) may include time delay materials known in the art, such as glyceryl
30         monostearate or glyceryl distearate alone or with a wax. To prepare a capsule, it may be

advantageous to use lactose and a liquid carrier, such as high molecular weight polyethylene glycols.

Compositions and dosage forms prepared in accordance with the present invention optionally also may contain lactose, sodium citrate, calcium carbonate, dicalcium

5      phosphate and disintegrating agents such as starch, alginic acids and certain complex silica gels combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets, troches, pills, capsules and the like.

Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated

10     with shellac, sugar or both. When aqueous suspensions are used they may contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyols such as polyethylene glycol, propylene glycol and glycerol, and chloroform or mixtures thereof also may be used. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

15     The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils.

20     The aqueous solutions, also including solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation, microfiltration, and/or by various antibacterial and antifungal agents, for example, parabens, chlorobutanol,

25     phenol, sorbic acid, thimerosal, and the like.

Examples of injectable dosage forms include sterile injectable liquids, e.g., solutions, emulsions and suspensions. Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered

30     sterilization. Generally, dispersions are prepared by incorporating the various sterilized

active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation may include vacuum drying and a freeze-dry technique that yields a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

Examples of injectable solids include powders that are reconstituted, dissolved or suspended in a liquid prior to injection. In injectable compositions, the carrier typically includes sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included within the compositions of the present invention.

Solid dosage forms include dosage forms for rectal administration, which include suppositories formulated in accordance with known methods and containing at least one compound of the present invention. Examples of solid carriers include lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like.

Topical administration, in the form of gels (water or alcohol based), creams or ointments, for example, containing compounds of the invention may be used. Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders. Such topical formulations can be used for example, to treat ocular diseases as well as inflammatory diseases such as rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions and the like.

Compounds of the invention also may be incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through transdermal barrier.

For administration by inhalation, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Compositions according to the invention also may be formulated in a manner that resists rapid clearance from the vascular (arterial or venous) wall by convection and/or diffusion, thereby increasing the residence time of the compound at the desired site of

action. A periadventitial depot comprising a compound according to the invention may be used for sustained release. One such useful depot for administering a compound according to the invention may be a copolymer matrix, such as ethylene-vinyl acetate, or a polyvinyl alcohol gel surrounded by a Silastic shell. Alternatively, a compound according to the

5      invention may be delivered locally from a silicone polymer implanted in the adventitia.

An alternative approach for minimizing washout of a compound according to the invention during percutaneous, transvascular delivery comprises the use of nondiffusible, drug-eluting microparticles. The microparticles may be made from any of a variety of synthetic polymers, such as polylactide, or natural substances, including proteins or

10     polysaccharides. Such microparticles enable strategic manipulation of variables including total dose of drug and kinetics of its release. Microparticles can be injected efficiently into the arterial or venous wall through a porous balloon catheter or a balloon over stent, and are retained in the vascular wall and the periadventitial tissue for at least about two weeks. Formulations and methodologies for local, intravascular site-specific delivery of

15     therapeutic agents are discussed in Reissen et al. (*J. Am. Coll. Cardiol.* 1994; 23: 1234-1244). A channeled balloon catheter (such as "channelled balloon angioplasty catheter", Mansfield Medical, Boston Scientific Corp., Watertown, Mass.) may be used. This catheter includes a conventional balloon covered with a layer of 24 perforated channels that are perfused via an independent lumen through an additional infusion orifice.

20     Various types of balloon catheters, such as double balloon, porous balloon, microporous balloon, channel balloon, balloon over stent and hydrogel catheters, all of which may be used to practice the invention, are disclosed in Reissen et al. (1994).

Another embodiment of the invention provides a compound according to the invention to be administered by means of perfusion balloons. These perfusion balloons,

25     which make it possible to maintain a blood flow and thus to decrease the risks of ischaemia of the myocardium, on inflation of the balloon, also enable the compound to be delivered locally at normal pressure for a relatively long time, more than twenty minutes, which may be necessary for its optimal action.

A composition according to the invention also may comprise a hydrogel which is

30     prepared from any biocompatible or non-cytotoxic (homo or hetero) polymer, such as a

hydrophilic polyacrylic acid polymer that can act as a drug absorbing sponge. Such polymers have been described, for example, in application WO 93/08845. Certain of them, such as, in particular, those obtained from ethylene and/or propylene oxide are commercially available.

5        Another aspect of the present invention relates to a pharmaceutical composition including a compound according to the invention and poloxamer, such as Poloxamer 407, which is a non-toxic, biocompatible polyol, commercially available (e.g., from BASF, Parsippany, N.J.). A poloxamer impregnated with a compound according to the invention may be deposited for example, directly on the surface of the tissue to be treated, for

10      example during a surgical intervention. Poloxamer possesses essentially the same advantages as hydrogel while having a lower viscosity. The use of a channel balloon catheter with a poloxamer impregnated with a compound according to the invention may be advantageous in that it may keep the balloon inflated for a longer period of time, while retaining the properties of facilitated sliding, and of site-specificity of the poloxamer.

15      The composition also may be administered to a patient via a stent device. In this embodiment, the composition is a polymeric material in which the compound of the invention is incorporated, which composition is applied to at least one surface of the stent device.

        Polymeric materials suitable for incorporating the compound of the invention

20      include polymers having relatively low processing temperatures such as polycaprolactone, poly(ethylene-co-vinyl acetate) or poly(vinyl acetate or silicone gum rubber and polymers having similar relatively low processing temperatures. Other suitable polymers include non-degradable polymers capable of carrying and delivering therapeutic drugs such as latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers

25      (SEBS) and biodegradable, bioabsorbable polymers capable of carrying and delivering therapeutic drugs, such as poly-DL-lactic acid (DL-PLA), and poly-L-lactic acid (L-PLA), polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes.

        The compounds of the present invention also may be formulated for use in conjunction with other therapeutically active compounds or in connection with the

30      application of therapeutic techniques to address pharmacological conditions, which may be

ameliorated through the application of a compound according to the present invention.

The percentage of active ingredient in the compositions of the invention may be varied. Several unit dosage forms may be administered at about the same time. A suitable dose employed may be determined by a physician or qualified medical professional, and

5    depends upon various factors including the desired therapeutic effect, the nature of the illness being treated, the route of administration, the duration of the treatment, and the condition of the patient, such as age, weight, general state of health and other characteristics, which can influence the efficacy of the compound according to the invention. In adults, doses are generally from about 0.001 to about 50, preferably about

10    0.001 to about 5, mg/kg body weight per day by inhalation; from about 0.01 to about 100, preferably 0.1 to 70, more preferably 0.5 to 10, mg/kg body weight per day by oral administration; from about 0.1 to about 150 mg applied externally; and from about 0.001 to about 10, preferably 0.01 to 10, mg/kg body weight per day by intravenous or

15    Method of the Invention.

The compounds of the present invention inhibit or regulate phosphorylation events. Tyrosine kinase inhibition may be determined by measuring the autophosphorylation level of recombinant kinase receptor, and/or phosphorylation of natural or synthetic substrates. Phosphorylation can be detected, for example, using an antibody specific for

20    phosphotyrosine in an ELISA assay or on a western blot. Some assays for tyrosine kinase activity are described in Panek et al., J. *Pharmacol. Exp. Thera.*, 283: 1433-44 (1997) and Batley et al., *Life Sci.*, 62: 143-50 (1998).    Detailed descriptions of conventional assays, such as those employed in phosphorylation assays, can be obtained from numerous publications, including Sambrook, J. et al., *Molecular Cloning: A Laboratory Manual*, 2nd

25    ed. (Cold Spring Harbor Laboratory Press 198(. All references mentioned herein are incorporated in their entirety.

In addition, methods of detecting expression of proteins whose expression is regulated by tyrosine kinase activity can be used. These methods include immunohistochemistry (IHC) for detection of protein expression, fluorescence *in situ*

30    hybridization (FISH) for detection of gene amplification, competitive radioligand binding

assays, solid matrix blotting techniques, such as Northern and Southern blots, reverse transcriptase polymerase chain reaction (RT-PCR) and ELISA. See, e.g., Grandis et al., Cancer, 78:1284-1292. (1996); Shimizu et al., *Japan J. Cancer Res.*, 85:567-571 (1994); Sauter et al., *Am. J. Path.*, 148:1047-1053 (1996); Collins, *Glia*, 15:289-296 (1995);

5        Radinsky et al., Clin. *Cancer Res.*, 1:19-31 (1995); Petrides et al., *Cancer Res.*, 50:3934-3939 (1990); Hoffmann et al., *Anticancer Res.*, 17:4419-4426 (1997); Wikstrand et al., *Cancer Res.*, 55:3140-3148 (1995).

*In vivo* assays also can be utilized. For example, VEGF receptor tyrosine kinase inhibition can be observed by mitogenic assays using HUVEC cells (ATCC) stimulated

10       with VEGF in the presence and absence of inhibitor. Another method involves testing for inhibition of growth of VEGF-expressing tumor cells, using for example, human tumor cells injected into a mouse. (See, U.S. Patent No. 6,365,157 to Rockwell et al.)

Also included within the scope of the present invention are methods of inhibiting VEGF receptor tyrosine kinases, especially KDR, and/or treating or preventing VEGF

15       receptor kinase-dependent diseases and conditions in mammals using the VEGF receptor kinase inhibitors of Formula I. The VEGF receptor is usually bound to a cell, such as an endothelial or tumor cell. Alternatively, the VEGF receptor may be free from the cell.

According to the treatment method of the present invention, an effective anti-angiogenic amount of one or more compounds of Formula (I), or pro-drug thereof, is

20       administered to a mammal in need of such treatment. The diseases which may be treated or prevented by the present methods include, for example, those in which pathogenic angiogenesis or tumor growth is stimulated through a VEGF/VEGFR paracrine and/or autocrine loop. For example, paracrine VEGFR stimulation of vascular endothelium is associated with angiogenic diseases and vascularization of tumors. VEGF receptors are

25       also found on tumor cells, indicating the presence of an autocrine and/or paracrine loop in these cells. Thus, the method is also useful for neutralizing VEGF receptors on such cells, thereby inhibiting autocrine and/or paracrine stimulation and inhibiting tumor growth.

The compounds and compositions according to the invention may be administered as frequently as necessary as determined by a skilled practitioner in order to obtain the

30       desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose

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and may find much weaker maintenance doses adequate. For other patients, it may be
necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance
with the physiological requirements of each particular patient. Generally, the active
product may be administered orally 1 to 4 times per day. For other patients, it may be
5       necessary to prescribe not more than one or two doses per day.

Thus, the method is effective for treating subjects with tumors and neoplasms,
particularly where disease development involves angiogenesis. Tumors and neoplasms
include, for example, malignant tumors and neoplasms, such as blastomas, carcinomas or
sarcomas, and highly vascular tumors and neoplasms. Cancers that may be treated by the
10      methods of the present invention include, for example, cancers of the brain, genitourinary
tract, lymphatic system, stomach, renal, colon, larynx, lung and bone. Non-limiting
examples further include epidermoid tumors, squamous tumors, such as head and neck
tumors, colorectal tumors, prostate tumors, breast tumors, lung tumors, including lung
adenocarcinoma and small cell and non-small cell lung tumors, pancreatic tumors, thyroid
15      tumors, ovarian tumors, and liver tumors. The method is also useful for treatment of
vascularized skin cancers, including squamous cell carcinoma, basal cell carcinoma, and
skin cancers that can be treated by suppressing the growth of malignant keratinocytes, such
as human malignant keratinocytes. Other cancers that can be treated include Kaposi's
sarcoma, CNS neoplasms (neuroblastomas, capillary hemangioblastomas, meningiomas
20      and cerebral metastases), melanoma, gastrointestinal and renal carcinomas and sarcomas,
rhabdomyosarcoma, glioblastoma, including glioblastoma multiforme, histiocytic
lymphoma, and leiomyosarcoma.

The treatment method of this invention includes treatment or prevention of non-
neoplastic angiogenic dependent diseases like inflammatory diseases and other diseases
25      characterized by paracrine stimulation through VEGF receptors. Examples of
non-neoplastic angiogenic diseases include diseases characterized by retinal
vascularization, such as neovascular glaucoma, proliferative retinopathy, including diabetic
retinopathy, retinopathy of prematurity (retrolental fibroplastic), macular degeneration, and
corneal graft rejection. Examples of inflammatory diseases that may be treated include,
30      but are not limited to, atherosclerosis, rheumatoid arthritis (RA), insulin-dependent

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diabetes mellitus, multiple sclerosis, myasthenia gravis, Chron's disease, autoimmune

nephritis, primary biliary cirrhosis, psoriasis, acute pancreatitis, allograph rejection,

allergic inflammation, contact dermatitis and delayed hypersensitivity reactions,

inflammatory-bowel disease, septic shock, osteoporosis, osteoarthritis, and cognition

5        defects induced by neuronal inflammation. The compounds of this invention are not the

first 1,2,4-triazoles found to have anti-inflammatory properties. In U.S. Patent No.

4,020,064, it is reported that 1,2,4-triazole compounds having certain acetamidyl

substituents on N-4 are useful as anti-inflammatory agents. Other non-limiting examples

of angiogenic diseases are hemangiomas, angiofibromas, Osler-Weber syndrome,

10        restinosis, and fungal, parasitic and viral infections, including cytomegaloviral infections.

The treatment method of the present invention also includes treatment of tumors

that express VEGF receptors (*e.g.* KDR), for example through inhibition of an autocrine

VEGF/VEGFR loop, wherein one or more of the Formula I compounds are administered in

an amount effective to reduce tumor growth or size. The method can be used to treat a

15        solid or liquid tumor that is not vascularized, or is not yet substantially vascularized.

Examples of solid tumors which may be accordingly treated include breast carcinoma, lung

carcinoma, colorectal carcinoma, pancreatic carcinoma, glioma and lymphoma. Examples

of liquid tumors include leukemia, multiple myeloma and lymphoma. Some examples of

leukemias include acute myelogenous leukemia (AML), chronic myelogenous leukemia

20        (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL),

erythrocytic leukemia or monocytic leukemia. Some examples of lymphomas include

Hodgkin's and non-Hodgkin's lymphoma.

Moreover, included within the scope of the present invention is use of the present

inventive compounds in vivo and in vitro for investigative, diagnostic, or prophylactic

25        methods, which are well known in the art.

In the methods of the present invention, an effective anti-angiogenic amount of one

or more of the Formula (I) compounds, including salts and solvates, is administered to a

mammal in need. The term "administering" as used herein means delivering the

compounds of the present invention to a mammal by any method that may achieve the

30        result sought. They may be administered, for example, orally, parenterally (intravenously

or intramuscularly), topically, transdermally or by inhalation. The term "mammal" as used herein is intended to include, but is not limited to, humans, laboratory animals, domestic pets and farm animals. "Effective anti-angiogenic amount" means an amount of compound of the present invention that when administered to a mammal influences the progression of

5     an angiogenic dependent disease. The influence is mediated through a slowing or arrest of pathogenic neovascularization around diseased cells. Accordingly, the influence may be a prevention or arrest of neovascularization that leads to the death of diseased cells and eradication of the disease from the body. However, the influence will be therapeutically beneficial even when not so far-reaching. Thus, as the term is used in this disclosure,

10    "influencing the progression of the angiogenic disease" includes causing the progression of the disease to be slowed by partial or complete restriction of the blood supply to diseased cells, resulting in an increase in life expectancy of the mammal afflicted with the disease.

Having thus described the present invention with reference to certain preferred embodiments, the invention will now be further illustrated by the following non-limiting

15    examples.

## EXAMPLES

### Example 1

### Preparation of Ethyl Benzimidate Hydrochloride (A)
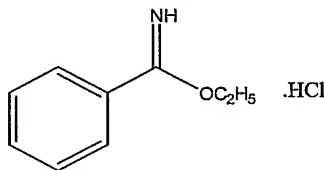


20    Dry HCl (g) was bubbled through a solution of benzonitrile in absolute ethanol for 4 h. A white precipitate formed and was collected by filtration, washed with absolute ethanol and dried under high vacuum to give the title compound in nearly quantitative yield.

25

## Example 2

### Preparation of Benzamidine Hydrochloride (**B**)
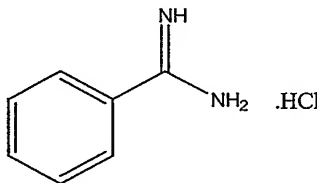


A slight molar excess of dry ammonia gas was bubbled through a solution of ethyl

5    benzimidate hydrochloride in absolute ethanol.  The mixture was stirred at room

temperature for 3 h.  Ammonium chloride produced from the excess ammonia was

removed by filtration and the filtrate was collected and concentrated. The residue was

recrystallized from ethanol, filtered and dried under high vacuum to give the title

compound in nearly quantitative yield.

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## Example 3

### Preparation of Ethyl 2-[(4-Pyridinyl)methylamino]benzoate (**C**)



15 ,
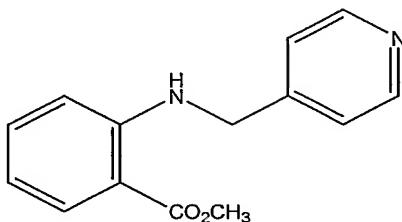
A mixture of methyl anthranilate (7.5 g) and 4-pyridinylcarboxaldehyde (8.6 g) in

MeOH (300 mL) and acetic acid (3 mL) was stirred at room temperature for 12 h.  Sodium

cyanoborohydride ($NaBH_3CN$) (6.9 g) was added to the reaction mixture and the resulting

solution was stirred at r.t. for 12 h.  The reaction mixture was then concentrated and the

20    residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ and brine. The

organic layer was dried with $MgSO_4$, filtered, concentrated and purified by flash

chromatography over $SiO_2$ (1:1 ethyl acetate/hexane) to give the title compound (10.2 g,

50%).

Example 4

Preparation of 2-[(4-Pyridinyl)methylamino]benzoic Acid Hydrazide (D)
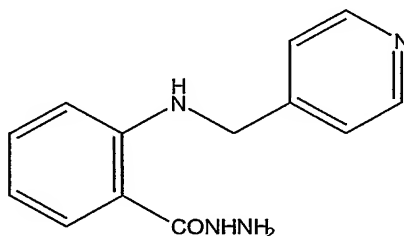


5          A mixture of Ethyl 2-[(4-pyridinyl)methylamino]benzoate (10 g) in hydrazine (50

ml) was refluxed.  After 2 h the excess hydrazine was removed and the remaining mixture

was dissolved in dichloromethane, washed with brine and dried with MgSO$_4$ and

concentrated. The crude residue was purified by flash chromatography to give the title

compound as a white solid (9.2 g, 97%).

10

Example 5

Preparation of 2-[2-(4-Pyridinyl)methylamino]phenyl-4-phenyl-1,2,4-triazole (1)
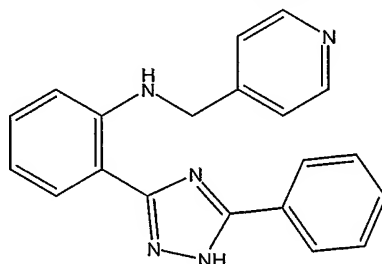


15

        A solution of sodium methylate (0.32 g, 6 mmol) in anhydrous ethanol (6 ml) was

added to a solution of the benzamidine hydrochloride B prepared in Example 2 (0.7 g, 4.5

mmol) in anhydrous ethanol (7 ml) at room temperature. The milky slurry was stirred at

room temperature for 45 min. and filtered. 2-[(4-Pyridinyl)methylamino]benzoic acid

20    hydrazide D prepared in Example 4 (0.73 g, 3 mmol) was then added to the ethanol filtrate

and the resulting yellow solution was refluxed for 2 hours. The ethanol was evaporated off

and the residue was re-dissolved in chlorobenzene, the resulting solution was refluxed

overnight. The mixture was cooled to room temperature and evaporated under vacuum.

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The solid residue was washed with water and recrystallized from ethanol to give the title compound (0.9 g, 91%) as a white solid. Its structure was confirmed by NMR and elemental analysis. $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.8 (br. s, 1H), 8.7 (m, 3H), 8.2 (m, 3H), 7.5 (m, 5H), 7.3 (t, 1H), 6.7 (m, 2H), 4.6 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 150.1, 149.4, 146.4, 131.2, 130.0, 129.2, 128.0, 126.4, 122.6, 115.0, 111.8, 45.7; MS 328.2 (M+H$^+$); Formula $C_{20}H_{17}N_5$ + 0.25H$_2$O, Calculated C 72.39, Found C 72.82, Calculated H 5.32, Found H 5.22, Calculated N 21.09, Found N 21.07.

Other 1,2,4-triazoles of this invention can be made by procedures analogous to those of Examples 1-5.

## Example 6

### Preparation of Compound (114)
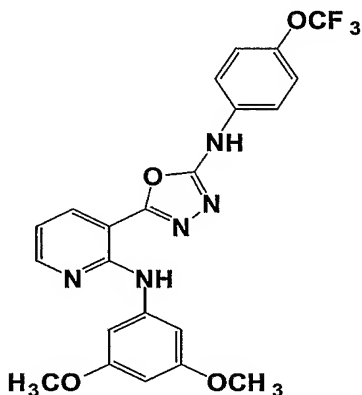


To a solution of 2-(3,5-dimethoxyphenylamino)nicotinic acid hydrazide(1.0g, 3.48 mmol) in dichloromethane (20 mL) was added 4-trifluoromethoxy phenyl isothiocyanate (0.64 mL, 3.83 mmol). The reaction mixture was refluxed for 2 hours under argon. The reaction mixture was allowed to cool and a solid precipitated from the solution, filtered, the solid was washed with ether to provide a yellow solid 1.489 g. Yield: 93%. $^1$H NMR (DMSO-$d_6$) δ 10.95 (s, 1H), 10.71 (s, 1H), 9.93-9.96 (m, 2H), 8.45-8.48 (m, 1H), 8.25-8.28 (m, 1H), 7.60-7.66 (m, 2H), 7.35-7.42 (m, 2H), 6.90-7.05 (m, 3H), 6.20 (s, 1H), 3.80 (s, 6H). MS m/z: 508.

To this yellow solid (1.45 g, 2.86 mmol) in toluene (20 mL) was added 1,3-dicyclohexylcarbodiimide (0.885 g, 4.3 mmol). Then, the reaction mixture was refluxed for 5 hours. The reaction mixture was diluted with ethyl acetate (50 mL), washed with aqueous sodium bicarbonate (30 mL) and brine (2x30 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The dried solution was filtered and evaporated to give a solid. This solid was washed with warm methanol to get a white solid (1.1 g, 81.5% yield). $^1$H NMR (DMSO-$d_6$) δ 11.10 (s, 1H), 10.06 (s, 1H), 8.42-8.44 (m, 1H), 8.06-8.09 (m, 1 H), 7.76-7.80 (m, 2H), 7.43-7.46 (d, 2H), 7.04-7.08 (m, 3H), 6.25-6.26 (t, 1H), 3.81 (t, 6H). Ms m/z: 474.

Other 1,3,4-oxadiazoles of this invention can be made by procedures analogous to those of Example 6

## Example 7

Preparation of 2-(3,5-dimethoxyphenylamino)nicotinic acid hydrazide (E)
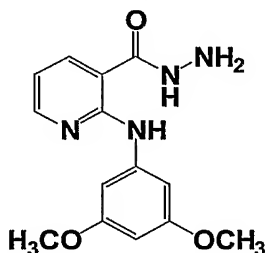


2-Chloropyridine-3-carboxylic acid (25 g) was refluxed in 200 mL of benzene and 150 mL of SOCl2. The solution was concentrated and chased with toluene. The residue obtained was refluxed in 100 mL of ethanol for 20 minutes. The solvents were removed under vacuum to give the pure product, 2-chloro-nicotinic acid ethyl ester. Light yellow oil; yield 72%; $^1$H NMR (CDCl$_3$) δ 1.42 (t, J = 6.6 Hz, 3H), 4.43(q, J = 6.8Hz, 2H), 7.37 (br s, 1H), 8.18 (d, J = 6.6Hz, 1H), 8.54 (s, 1H); $^{13}$C NMR δ 13.8, 61.8, 122.0, 126.9, 140.0, 149.5, 151.4, 164.2.

2-Chloro-nicotinic acid ethyl ester (2 mmol, 0.343g) and 3,5-dimethoxyaniline (2mmol, 0.306g) were dissolved in ethylene glycol (10mL) and heated to 160 °C with

stirring. The reaction mixture was maintained at this temperature for 6h. HCl gas evolved during the course of the reaction. On cooling, the reaction mixture was poured into water (10 mL) and extracted with ether (4 x 100 mL). The ethereal layer was dried over $MgSO_4$, evaporated and the residue was distilled at 162-165 °C/0.5 mm Hg. The product,2-(3,5-

5     dimethoxyphenylamino)nicotinic acid ethyl ester, was used in the next step without further purification. Yellow oil, yield 63%; $^1$H NMR ($CDCl_3$) δ 1.24 (t, $J$ = 7.1 Hz, 3H), 3.78 (s, 6H), 4.11 (t, $J$ = 7.1 Hz, 2H), 6.17 (s, 1H), 6.68 (t, $J$ = 6.0 Hz, 1H), 6.97 (s, 2H), 8.20 (d, $J$ = 7.7 Hz, 1H), 8.36 (s, 1H), 10.24 (s, 1H); $^{13}$C NMR δ 20.7, 55.0, 60.1, 94.8, 98.7, 103.2, 107.1, 113.1, 139.9, 141.2, 152.7, 155.8, 160.7, 167.2, 170.9.

10          2-(3,5-Dimethoxyphenylamino)nicotinic acid ethyl ester (1.94 mmol, 560mg) and 85% hydrazine hydrate (1.18 mL) and 2-propanol (2 mL) were refluxed for 3 h. On cooling, the red solution deposited a yellow solid that was filtered off and washed with a little 2-propanol. Compound **E** appeared as a yellow solid, 84% yield: $^1$H NMR (DMSO-$d_6$) δ 1.22 (br s, 2H), 4.00 (s, 6H), 6.18 (t, $J$ = 2.2 Hz, 1H), 6.66–6.70 (m, 1H), 6.94 (s,

15     2H), 7.64 (dd, $J$ = 1.8 Hz, 7.7 Hz, 1H), 7.70 (br s, 1H), 8.33 (dd, $J$ = 1.5 Hz, 4.8 Hz), 10.1 (br s, 1H); $^{13}$C NMR δ 55.3, 94.8, 98.7, 100.2, 103.4, 100.4, 109.5, 113.1, 135.1, 141.5, 151.8, 160.9, 169.1.

Example 8

20     (3,5-Dimethoxyphenyl)-*S*-Methylisothiourea Hydroiodide (F)
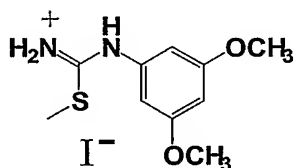


4-Fluorobenzoyl chloride (1.03 g, 6.5 mmol) was added dropwise to a vigorously stirred hot solution of anhydrous ammonium thiocyanate (0.61 g, 7.8 mmol) in dry acetone

25     (20 mL). The reaction mixture was refluxed for 5 min. Then, a solution of 3,5-dimethoxyaniline (1.0 g, 6.5 mmol) in dry acetone (10 mL) was added dropwise. The

reaction mixture was heated for 1 h. The solvent was evaporated and water (50 mL) was added to the residue. The precipitate was collected and recrystallized from ethyl alcohol to give the product, *N*-(3,5-dimethoxyphenyl)-N'-(4-fluorobenzoyl)thiourea. White needles (ethanol), Yield 69%; $^1$H NMR (DMSO) δ 3.76 (s, 6H), 6.43 (br s, 1H), 6.99 (br s, 2H), 7.35–7.41 (m, 2H), 8.04–8.09 (m, 2H), 11.62 (s, 1H) ; $^{13}$C NMR (DMSO) δ . Anal. Calcd for $C_{16}H_{15}FN_2O_3S$: C, 57.47; H, 4.52; N, 8.38. Found: C, 57.49; H, 4.43; N, 8.26.

        *N*-(3,5-Dimethoxyphenyl)-N'-(4-fluorobenzoyl)thiourea (1.5 g, 4.4 mmol) was heated to reflux with 5% aqueous NaOH (10 mL) for 15 min. The cooled reaction mixture was treated with concentrated HCl until acidic to precipitate both 4-fluorobenzoic acid and N-(3,5-dimethoxyphenyl)thiourea. The mixture was then made basic (pH 9) with concentrated $NH_4OH$ to dissolve the 4-fluorobenzoic acid. The product was filtered and recrystallized from 95% ethyl alcohol to give the pure product, N-(3,5-dimethoxyphenyl)thiourea . White prisms, yield 75%; $^1$H NMR (DMSO) δ 3.72 (s, 6H), 6.27 (br s, 1H), 6.62 (br s, 2H), 7.53 (br s, 2H), 9.66 (s, 1H); $^{13}$C NMR (DMSO) δ 55.2, 96.4, 100.8, 140.6, 160.4, 180.7. Anal. Calcd for C9H12N2O2S: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.66; N, 12.96.

        A solution of N-(3,5-dimethoxyphenyl)thiourea (0.53 g, 2.5 mmol) in freshly distilled dry methanol (10 mL) was treated with $CH_3I$ (0.36 g, 2.5 mmol). The solution was refluxed for 2h, cooled, and evaporated to dryness under vacuum. The crystalline product was washed with several portion of ethyl ether and dried to give pure Compound **F** which appeared as white microcrystals; yield 92%; $^1$H NMR (DMSO) δ 2.70 (s, 3H), 3.78 (s, 6H), 6.53–6.56 (m, 3H), 9.30 (br s, 2H); $^{13}$C NMR (DMSO) δ 55.6, 100.1, 103.7, 136.5, 161.1, 169.1.

Example 9

Preparation of (3,5-Dimethoxyphenyl)-{3-[5-(3,5-dimethoxy-phenylamino)-2H-[1,2,4]triazol-3-yl]-pyridin-2-yl}amine (**154**)



5
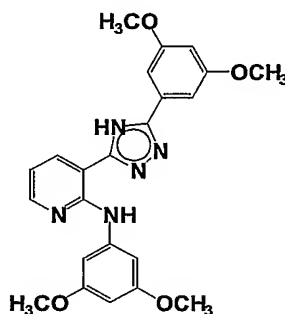
A solution of 2-(3,5-dimethoxyphenylamino)nicotinic acid hydrazide (**E**) (1mmol) and – (3,5-dimethoxyphenyl)-*S*-methylisothiourea hydroiodide (**F**) (1mmol) in 1 mL of pyridine were refluxed for 6 h. The cooled mixture was poured into crushed ice and

10    extracted with ether. The solvent was removed and the crude product was recrystallized from ethyl acetate (and two drops of ethanol) to give the pure product. Brown solid; yield 25%; $^1$H NMR (DMSO-$d_6$, 100 °C) δ 3.75 (s, 3H), 3.76 (s, 3H), 6.11 (br s, 1H), 6.18 (t, $J$ = 2.2 Hz, 1H), 6.81 (d, $J$ = 2.2 Hz, 2H), 6.89–6.93 (m, 1H), 7.07 (d, $J$ = 1.8 Hz, 2H), 8.28–8.29 (m, 2H), 9.22 (br s, 1H), 10.7 (br s, 1H).

15

Other 1,2,4-triazoles of the present invention can be prepared by procedures analogous to those of Examples 7-9.

Example 10

Preparation of 3-(Trifluoromethyl)phenacyl Bromide (G)

CF₃

Br

O
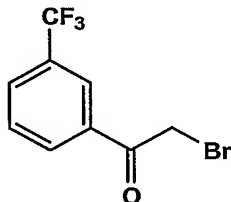
A solution of 3-(trifluoromethyl)acetophenone (25 g, 0.133 mol) in diethyl ether (20 ml) was cooled to 0°C. Aluminium chloride (0.15 g) was added in one portion, with stirring, followed by dropwise addition of bromine (6.85 ml, 0.133 mol), and the reaction mixture was allowed to reach room temperature overnight. Solvent was removed under vacuum and the crude product purified by distillation (94-97°C, 1mm Hg). The title compound was obtained as a colorless liquid (20.2g, 57%).

Example 11

Preparation of 2-Nitrobenzamidine hydrochloride (H)

NH       .HCl

NH₂

NO₂
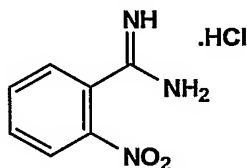
A solution of 2-nitrobenzonitrile (12.3 g, 0.083 mol) in THF (60 ml) was added dropwise with stirring to a cooled (0°C) solution of LiHMDS (1M in THF; 99.6 ml, 0.0996 mol) in ether (60 ml) and the reaction mixture allowed to warm to room temperature overnight. The reaction was quenched at 0°C with ethereal HCl (~150 ml). A brown semi-solid formed and the solvent was decanted off. The crude product was triturated with ether (~200 ml) and collected by filtration. After washing with ether (~1L) the title compound was obtained as a tan solid (~20 g, >100%, *i.e.* inorganic salts present).

Example 12

Preparation of 2-[5-(3-trifluoromethylphenyl)-1*H*-imidazol-2-yl]nitrobenzene (**I**)



5
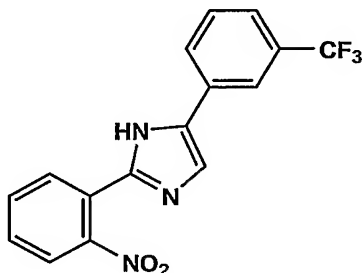
A mixture of compound **H** (13.78 g, 68.4 mmol), DMF (300 ml), compound **G** (18.27 g, 68.4 mmol), sodium iodide (~1 g) and triethylamine (19 ml, 136.8 mmol) was heated at 120°C for 48 hrs. Solvent was removed under vacuum and the residue dissolved in ethyl acetate (150 ml) and washed with water (3 x 200 ml) and then brine (200 ml),

10     dried (MgSO$_4$) and the solvent removed under vacuum. The crude product obtained was purified by 'dry flash' chromatography [Methanol/dichloromethane (1:99) – (3:97)]. Solvent was removed under vacuum and the residue dissolved in ethanol (~100 ml) and heated with activated charcoal for a few minutes then filtered through Celite. Solvent was removed under vacuum and the residue was purified by 'flash' chromatography [Methanol/

15     dichloromethane (1:99) – (3:97)]. The title compound was obtained as an orange/yellow glassy solid (7 g, 25% over 2 steps).

Example 13

Preparation of  2-[5-(3-trifluoromethylphenyl)-1$H$-imidazol-2-yl]aniline (**217**)
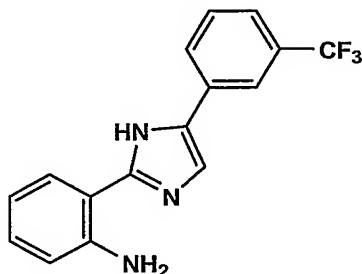


5        A mixture of compound **H** (6.25 g, 0.0188 mol), ethanol (350 ml) and palladium on carbon (5% wt) (1.25 g) was stirred under an atmosphere of hydrogen at room temperature overnight. The catalyst was filtered off through Celite and washed with ethanol (200 ml). Solvent was removed under vacuum to give an orange solid. This was washed with dichloromethane/petrol [200 ml, (1:1)] and the solid that remained was collected by

10      filtration. The title compound (1.1 g, 20%) was obtained as an off-white solid after recrystallisation from dichloromethane/petrol/methanol. MS m/z:  304 (M+H$^+$)

Other imidazoles of the present invention can be prepared by procedures analogous to those of Examples 10-13.

15

Example 14

Preparation of 2-Aminobenzamidoxime (**J**)
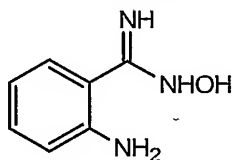


20      2-Aminobenzonitrile hydrochloride (50 g, 0.324 mol) was suspended in anhydrous methanol in a 2 L three necked flask. One mole equivalent of sodium methoxide (17.5 g, 0.324 mol) was added portionwise to the mixture (during the addition the temperature rose to 35°C). The reaction mixture was then stirred for 30 minutes at room temperature and a second equivalent of sodium methoxide (17.5 g, 0.324 mol) was added portionwise.  After

stirring for 30 minutes at room temperature, hydroxylamine hydrochloride (22.5 g, 0.324 mol) was added and the mixture heated under reflux for 20 hours. The mixture was concentrated and the residue partitioned between EtOAc (500 ml) and 2N sodium hydroxide (500 ml). The basic phase was separated and extracted with EtOAc (4 x 500 ml). The combined organic extract was washed with brine (4 x 500 ml) and dried over magnesium sulphate. After filtration and evaporation, a brown oil was obtained. Dry flash chromatography on silica gel [dichloromethane/ethanol (95:5)] followed by precipitation from dichloromethane/petroleum ether afforded the 2-aminobenzamidoxime (J) as a pale brown solid (31 g, 63%).

Example 15

Preparation of 2-Aminobenzamidine Dihydrochloride (K)
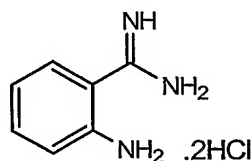


Following generally the method described in *J. Med. Chem.* **2003**, *46*, 913-916, a suspension of 2-aminobenzamidoxime (J) (31 g, 0.205 mol) and wet Raney nickel (50% slurry in water) (ca. 15 g) in EtOH (350 ml) was stirred under 3 atmospheres of hydrogen at 60°C for 16 hours. The catalyst was removed by filtration through a pad of celite and the cake was washed with EtOH (300 ml). The solvent was evaporated to give a brown oil, 2-aminobenzamidine (250 MHz $^1$H NMR in CDCl$_3$ consistent with structure). This material was dissolved in ethanol (200 ml) and 2N HCl in ether (230 ml, 0.46 mol) was added dropwise (during the addition the temperature rose to 35°C). The resulting precipitate was collected by filtration and dried under vacuum to give 2-aminobenzamidine dihydrochloride (K) as an off-white powder (37 g, 87%).

Example 16

General Procedure for Preparing 2-(5-Aryl-*1H*-[1,2,4]-triazol-3-yl)anilines (**218-222, 224-226**)



5
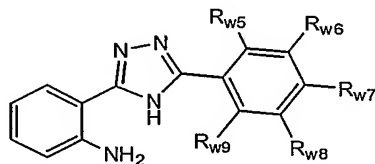
In a dry 100 ml three necked flask, 2-aminobenzamidine dihydrochloride (**K**) (12.0-16.9 mmol) was suspended in dry EtOH (18-20 ml) under nitrogen. A freshly prepared solution of sodium methoxide (2.3 eq.) in EtOH (30-35 ml) was added to the reaction mixture. The brown slurry was stirred at room temperature for 1 hour and filtered.

10 To the ethanol filtrate was added the appropriate arylcarboxylic acid hydrazide (1 eq.) and the reaction mixture heated under reflux for 3-6 hours. The solvent was evaporated under vacuum and the brown residue was dissolved in chlorobenzene (35-45 ml). The flask was equipped with a Dean-stark trap and the reaction mixture was heated under reflux overnight. After cooling to room temperature, the solvent was evaporated under vacuum.

15 The brown residue was purified by dry flash chromatography on silica gel [dichloromethane/methanol (99:1) – (95:5)], followed by trituration from dichloromethane/petroleum ether and recrystallisation from the appropriate solvent to give the corresponding triazole.

Although most of the arylcarboxylic acid hydrazides used to prepare compounds

20 **218-222** and **224-226** are commercially available, the 3-trifluoromethoxy-benzene–1-carbohydrazide was prepared in our laboratory. It was prepared as follows. 3-(Trifluoromethoxy)-methylbenzoate (5.0g, 22.7 mmol) was dissolved in dry MeOH (20mL) under nitrogen. Hydrazine monohydrate (2.27g, 45.4 mmol, 2 eq.) was added dropwise and the mixture was heated under reflux for 3 hours. The reaction mixture was

25 then concentrated under vacuum to give a solid. Water was removed by azeotroping with EtOH (x2), to leave an off-white solid (5.4 g, quantitative).

79

Example 17

Preparation of 2-(2-Nitrobenzyl)-4-(3-trifluoromethylbenzyl)-5-methylimidazole (L)
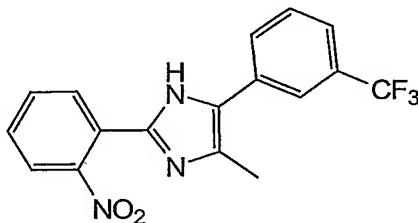


5           1-(3-Trifluoromethyl(benzyl))-1,2-propandione (4.80 g, 22.2 mmol) was dissolved in acetic acid (250mL) under nitrogen. 2-Nitrobenzaldehyde (3.69 g, 24.4 mmol, 1.1 eq.) and ammonium acetate (34.21 g, 444 mmol, 20 eq.) were added and the resulting mixture was heated at 100°C overnight. TLC analysis (EtOAc/$i$-Hexane, 3:7) showed no starting material remained so the resulting solution was concentrated to approx. 50mL and the

10          remaining acetic acid was neutralized with NaHCO$_3$ (solid and saturated solution). Ethyl acetate (300mL) was added and the phases separated. The aqueous layer was back-extracted with EtOAc (2x 250mL). The combined organic layers were washed with brine (250mL), dried (MgSO$_4$) and concentrated under vacuum to give a dark oil. Flash column chromatography [Acetone/$i$-Hexane (2:8)] provided the nitro-imidazole L as a dark orange

15          oil (4.8g, 62%).

Example 18

Preparation of 2-(4-methyl-5-(3-trifluoromethylphenyl)-1H-imidazol-2-yl)aniline (223)
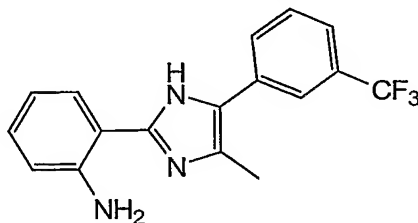


20

          2-(2-Nitrobenzyl)-4(3-trifluoromethylbenzyl)-5-methylimidazole (M) (2.5 g, 7.2 mmol) was dissolved in EtOH (60mL) and water (10mL). Iron powder (3.63 g, 9 eq.) and ammonium chloride (0.77 g, 14.4 mmol, 2 eq.) were added and the resulting suspension was heated under reflux for 3 hours. More ammonium chloride (0.77 g, 2 eq.) was added

and the heating was continued overnight. The reaction mixture was then concentrated and the residue partitioned between dichloromethane (75mL) and saturated NaHCO$_3$ (aq.) (50mL). The aqueous layer was back-extracted with dichloromethane (2x 50mL). The combined organic layers were washed with water (75mL), dried (MgSO$_4$), filtered and

5  concentrated under vacuum to give an orange solid. This material was recrystallised twice [dichloromethane/$i$-Hexane (1:1)] to give compound **223** as a pale orange crystalline solid (1.25g, 55%). MS m/z: 318 (M+H$^+$)

10  Analytical Data for Selected Compounds

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(3-bromophenyl)-1,2,4-triazole (**2**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.8  (br. s, 1H), 8.7 (m, 3H), 8 (m, 9H), 6.7 (q, 2H), 4.7 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 150.1, 149.3, 146.4, 131.8, 131.4, 128.6, 127.6, 125.3, 122.5, 116.0, 112.0, 45.8; MS 406.1 (M+);  Formula C$_{20}$H$_{16}$BrN$_5$, Calculated

15  C 59.13, H 3.97, N 17.23;  Found C 58.95, H 3.94, N 17.11.

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(4-trifluoromethylphenyl)-1,2,4-triazole (**3**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.8  (br. s, 1H), 8.8 (br. s, 2H), 8.6 (d, 2H), 8.3 (d, 2H), 7.9 (m, 3H), 7.4 (d, 2H), 7.2 (t, 1H), 6.7 (m, 2H), 4.6 (d, 2H); $^{13}$C NMR (75 MHz,

20  DMSO-$d_6$) δ (ppm) 150.1, 149.4, 146.5, 131.9, 127.8, 127.0, 126.2, 122.7, 122.5, 116.0, 112.0, 45.7; MS 396.2 (M+H$^+$); Formula C$_{21}$H$_{16}$F$_3$N$_5$, Calculated C 63.79, H 4.08, N 17.7; Found C 63.85, H 4.18, N 17.57.

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(3-chlorophenyl)-1,2,4-triazole (**4**): $^1$H NMR

25  (300 MHz, DMSO-$d_6$) δ (ppm) 14.8  (br. s, 1H), 8.8 (m, 3H), 8.0 (m, 3H), 7.4 (m, 6H), 6.8 (q, 2H), 4.5 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 150.1, 149.3, 146.4, 134.0, 132.9, 131.2, 129.5, 127.8, 125.9, 124.9, 122.5, 116.0, 111.9, 45.8; MS 362.2 (M+H$^+$); Formula C$_{20}$H$_{16}$ClN$_5$, Calculated C 66.39, H 4.46, N 19.35; Found C 66.32, H 4.48, N 19.31.

30

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(4-biphenyl)-1,2,4-triazole (**5**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.8 (br. s, 1H), 8.8 (br. s, 1H), 8.6 (m, 1H), 8.3 (m, 3H), 7.9 (m, 6H), 7.3 (m, 6H), 6.7 (m, 2H), 4.6 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 160.2, 155.5, 150.1, 149.4, 146.4, 141.1, 139.9, 133.5, 131.8, 130.6, 129.4, 128.7, 128.4, 127.4, 122.5, 116.0, 112.1, 109.2, 45.7; MS 404.2 (M+H$^+$); Formula $C_{26}H_{21}N_5$ + 0.25H$_2$O: Calculated C 76.55, H 5.31, N 17.15; Found C 76.67, H 5.20, N 16.25.

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(3-benzoxyphenyl)-1,2,4-triazole (**6**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 17H), 6.7 (m, 2H), 5.3 (s, 2H), 4.6 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 159.0, 150.1, 149.4, 146.4, 137.3, 130.3, 128.8, 128.2, 128.1, 127.6, 122.5, 118.9, 116.0, 112.5, 112.1, 69.7, 45.7; MS 434.2 (M+H$^+$); Formula $C_{27}H_{23}N_5O$: Calculated C 74.81, H 5.35, N 16.15; Found C 74.79, H 5.20, N 15.88.

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(4-benzoxyphenyl)-1,2,4-triazole (**7**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 17H), 6.6 (m, 2H), 5.3 (s, 2H), 4.6 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 159.9, 149.6, 149.0, 145.9, 136.7, 128.4, 127.8, 127.7, 115.5, 115.2, 115.0, 111.5, 111.0, 69.3, 45.3; MS 434.2 (M+H$^+$); Formula $C_{27}H_{23}N_5O$: Calculated C 74.81, H 5.35, N 16.15; Found C 74.78, H 5.34, N 16.12.

2-[2-(4-Pyridinyl)methylamino-5-chloro]phenyl-4-(3-trifluoromethylphenyl)-1,2,4-triazole (**8**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.8 (br. s, 1H), 8 (m, 17H), 6.7 (d, 1H), 4.7 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 150.1, 148.8, 145.2, 130.9, 130.6, 130.4, 130.3, 129.9, 129.5, 127.2, 126.6, 126.2, 122.5, 122.4, 119.6, 113.7, 45.8; MS 430.1 (M+H$^+$); Formula $C_{21}H_{15}ClF_3N_5O$, Calculated C 58.68, H 5.52, N 16.29; Found C 58.38, H 5.61, N 16.06.

2-[3-[2-(4-Pyridinyl)methylamino]pyridinyl]-4-(3-trifluoromethylphenyl)-1,2,4-triazole (**9**): $^1$H NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8.4 (m, 7H), 7.8 (m, 2H), 7.2 (d, 2H), 6.7 (m, 2H), 4.6 (d, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 153.6,

148.6, 148.5, 134.2, 129.2, 129.0, 128.9, 128.5, 128.1, 125.2, 124.8, 121.2, 121.0, 110.9,

42.3; MS 397.3 (M+H$^+$); Formula $C_{20}H_{15}F_3N_6$: Calculated C 60.61, H 3.81, N 21.19;

Found C 60.57, H 3.87, N 21.12.


5    2-[2-(4-Pyridinyl)methylamino]phenyl-4-(3-phenoxyphenyl)-1,2,4-triazole (**10**): $^1$H NMR

(300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 16H), 6.6 (m, 2H), 4.6 (d, 2H); $^{13}$C

NMR (75 MHz, DMSO-$d_6$) δ (ppm) 157.7, 156.9, 150.0, 149.2, 146.4, 131.0, 130.5, 124.2,

122.4, 121.4, 119.4, 116.0, 111.8, 45.6; MS 420.2 (M+H$^+$); Formula $C_{26}H_{21}N_5O$:

Calculated C 74.44, H 5.05, N 16.704; Found C 74.25, H 4.92, N 16.54.

10

2-[(4-Pyridinyl)methylamino]phenyl-4-(4-phenoxyphenyl)-1,2,4-triazole (**11**): $^1$H NMR

(300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 16H), 6.6 (m, 2H), 4.6 (d, 2H); $^{13}$C

NMR (75 MHz, DMSO-$d_6$) δ (ppm) 158.4, 156.4, 150.1, 149.4, 145.4, 130.5, 128.7, 128.4,

127.6, 126.6, 124.3, 122.6, 119.5, 115.9, 111.8, 45.7; MS 420.2 (M+H$^+$); Formula

15   $C_{26}H_{21}N_5O$: Calculated C 74.44, H 5.05, N 16.70; Found C 74.22, H 4.94, N 16.45.


2-[(4-Pyridinyl)methylamino]phenyl-4-(4-ethynylphenyl)-1,2,4-triazole (**12**): $^1$H NMR

(300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 12H), 6.6 (m, 2H), 4.7 (d, 2H), 4.4

(s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 150.1, 149.3, 146.4, 132.6, 131.5, 127.9,

20   126.5, 122.7, 122.5, 116.0, 111.9, 88.6, 82.5, 55.4, 45.7; MS 352.2 (M+H$^+$); Formula

$C_{22}H_{17}N_5 + 0.25H_2O$: Calculated C 74.25, H 4.96, N 19.67. Found C 74.23, H 5.09, N

19.14.


2-[(4-Pyridinyl)methylamino]phenyl-4-(3-biphenyl)-1,2,4-triazole (**13**): $^1$H NMR (300

25   MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 16H), 6.6 (m, 2H), 4.6 (d, 2H); $^{13}$C

NMR (75 MHz, DMSO-$d_6$) δ (ppm) 149.1, 148.3, 145.3, 140.2, 139.0, 130.1, 129.3, 128.9,

128.4, 127.3, 127.1, 127.0, 126.1, 124.6, 123.5, 121.5, 114.1, 110.8, 110.4, 45.7; MS 404.2

(M+H$^+$); Formula $C_{26}H_{21}N_5$: Calculated C 77.40, H 5.25, N 17.36. Found C 77.07, H 5.34,

N 17.24.

30

2-[(4-Pyridinyl)methylamino]phenyl-4-[3-(2-phenylethenyl)phenyl]-1,2,4-triazole (**14**): [1]H
NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 18H), 6.6 (m, 2H), 4.6 (d,
2H); ^{13}C NMR (75 MHz, DMSO-$d_6$) δ (ppm) 150.1, 149.3, 146.4, 138.0, 137.8, 133.7,
130.6, 129.7, 129.1, 128.7, 128.2, 127.4, 127.0, 126.9, 124.7, 122.6, 116.0, 111.9, 45.8;
MS 430.2 (M+H^{+}); Formula $C_{26}H_{21}N_5O$: Calculated C 78.30, H 5.40, N 16.31. Found C
78.30, H 5.40, N 16.16.

2-[(4-Pyridinyl)methylamino]phenyl-4-[3-[(*N,N*-dimethylaminomethyl)phenyl)-1,2,4-
triazole (**15**): ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.6 (m, 3H), 8.0 (d, 1H), 7.9 (m, 3H),
7.4 (m, 3H), 7.3 (m, 3H), 6.8 (t, 1H), 6.6 (d, 1H), 4.6 (s, 2H), 2.7 (t, 2H), 2.4 (m, 2H), 2.3
(s, 6H), 1.9 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 157.7, 157.2, 148.5, 148.3,
145.0, 141.2, 129.6, 128.5, 128.3, 127.5, 126.7, 125.1, 122.9, 121.2, 115.0, 110.6, 110.1,
57.8, 45.3, 43.9, 32.2, 27.5; MS 413.3 (M+H^{+}); $C_{25}H_{28}N_6$: Calculated: C, 69,75 %; H, 6.56
%; N, 19.51 %; Found: C, 69.33 %; H, 6.69 %; N, 19.41 %.

2-[(4-Pyridinyl)methylamino]phenyl-4-[4-[(*N,N*-dimethylaminopropyl)phenyl)-1,2,4-
triazole (**16**): ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.6 (m, 3H), 7.9 (m, 3H), 7.4 (d, 2H),
7.2 (m, 4H), 6.8 (t, 1H), 6.6 (d, 1H), 4.6 (s, 2H), 2.7 (t, 2H), 2.4 (m, 2H), 2.3 (s, 6H), 1.9
(m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 158.7, 158.1, 149.5, 149.3, 146.0, 143.4,
130.5, 128.5, 127.7, 127.1, 126.3, 122.2, 116.0, 111.6, 111.1, 58.8, 46.2, 45.0, 33.2, 28.5;
MS 413.3 (M+H^{+}); Formula $C_{25}H_{28}N_6$: Calculated: C 69.75 %, H 6.56 %, N 19.51 %;
Found: C 69.86 %, H 6.52 %, N, 19.39 %.

2-[2-(4-Pyridinyl)methylamino]phenyl-4-(3-trifluoromethylphenyl)-1,2,4-triazole (**18**): [1]H
NMR (300 MHz, DMSO-$d_6$) δ (ppm) 14.6 (br. s, 1H), 8 (m, 13H), 4.6 (d, 2H); MS 396.2
(M+H^{+}).

Compound (**19**): ^{1}H NMR (DMSO-$d_6$) δ (ppm) 8.89 (s, 1H), 8.15-8.35 (m, 4H), 7.98-8.02
(m, 2H), 7.00 (s, 1H), 7.10 (s, 2H), 6.68-6.78 (m, 1H), 6.00 (s, 2H), 4.67-4.69 (d, 2H), 3.28
(s, 3H); MS m/z: 450 (M+H^{+})

Compound (20): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.44 (s, 1H), 8.16 –8.45 (m, 2H), 7.65-7.75 (m, 2H), 6.68-7.15 (m, 5H), 6.06 (s, 2H), 4.65-4,67 (d, 2H), 3.83-3.90 (d, 6H); MS m/z: 432 (M+H$^+$)

5   Compound (21): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.72 (s, 1H), 8.18-8.50 (m, 3H), 7.44-7.65 (m, 3H), 7.08 (s, 1H), 6.72-6.77 (m, 1H), 6.60-6.61 (d, 2H), 6.41-6.42 (d, 1H), 4.70-4.71 (d, 2H), 3.71-3.81 (m, 9H); MS m/z: 418 (M+H$^+$)

Compound (22): 1H NMR (DMSO-$d_6$) δ (ppm) 14.21 (s, 1H), 8.52-8.56 (m, 2H), 7.98-
10   8.02 (m, 1H), 7.55-7.64(m, 2H), 7.34-7.38 (m, 2H), 7.22-7.26 (m, 1H), 7.06-7.10 (m, 1H), 4.62-4.64 (d, 2H), 3.72-3.88 (m, 6H); MS m/z: 388 (M+H$^+$)

Compound (23): 1H NMR (DMSO-$d_6$) δ (ppm) 8.55-8.61 (m, 3H), 7.90-7.98 (m, 1H), 7.55-7.64 (m, 2H), 7.35-7.40 (m, 2H), 7.16-7.24 (m, 1H), 6,64-6.72 (m, 2H), 6.10 (s, 2H),
15   4.60-4.62 (d, 2H); MS m/z: 372 (M+H$^+$)

Compound (24): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.63 (s, 1H), 8,53-8.59 (m, 3H), 8.08-8.24 (m, 2H), 7.91-7.94 (m, 1H), 7.54-7.60 (m, 1H), 7.40-7.42 (m, 2H), 6.65-6.75 (m, 2H), 4.63-4.65 (d, 2H); MS m/z: 380 (M+H$^+$)

20

Compound (25): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.60 (s, 1H), 8.61-8.72 (m, 3H), 7.90-8.04 (m, 3H), 7.20-7.71 (m, 5H), 6.62-6.84 (m, 2H), 4.64-4.68 (m, 2H); MS m/z: 346 (M+H$^+$)

Compound (26): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.71(s, 1H), 8.55-8.68 (m, 3H), 8.30-8.38
25   (m, 2H), 7.83-7.94 (m, 3H), 7.40-7.44 (m, 2H), 7.14-7.26 (m, 1H), 6.63-6.78 (m, 2H), 4.64-4.66 (d, 2H); MS m/z: 396 (M+H$^+$)

Compound (27): $^1$H NMR (DMSO-$d_6$) 10.59 (s, 1H), 8.50-8.53 (m, 2H), 7.97-8.00 (m, 1H), 7.62-7.64 (m, 1H), 7.24-7.36 (m, 3H), 6.88-6.89 (d, 2H), 6.67-6.68 (m, 2H), 6.20 (s,
30   1H), 4.66-4.68 (d, 2H), 3.76 (s, 6H); MS m/z 404 (M+H$^+$)

Compound (28): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.68-8.74 (m, 1H), 8.50-8.56 (m, 2H), 8.30-8.35 (m, 2H), 8.04-8.08 (m, 2H), 7.91-7.96 (m, 1H), 7.41-7.43 (m, 2H), 7.20-7.28 (m, 1H), 6.62-6.71 (m, 2H), 4.60-4.62 (d, 2H), 3.28 (s, 3H); MS m/z: 406 (M+H$^+$)

5

Compound (29): $^1$H NMR (DMSO-$d_6$) δ (ppm) 12.84(s, 1H), 9.33 (s, 1H), 8.82-8.86 (m, 1H), 8.40-8.44 (m, 1H), 7.98-8.08 (s, 1H), 7.30-7.82 (m, 6H), 6.92-6.99 (m, 1H), 6.74-6.78 (m, 1H), 4.37-4.39(d, 2H); MS m/z: 318 (M+H$^+$)

Compound (30): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.48-8.52 (m, 2H), 7.40-8.02 (m, 7H),
10        6.70-6.94 (m, 2H), 4.35-4.42 (d, 2H); MS m/z: 385 (M+H$^+$)

Compound (31): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.18-8.22 (m, 1H), 7.85-7.97 (m, 3H), 6.90-7.00 (m, 2H), 6.54-6.60 (m, 1H), 3.75-3.78 (m, 3H), 3.30-3.50 (m, 6H), 2.20-2.25 (m, 2H), 1.85-1.90 (m, 4H); MS m/z: 393 (M+H$^+$)

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Compound (32): $^1$H NMR (DMSO-$d_6$) δ (ppm) 12.69 (s, 1H), 7.96-7.98 (m, 2H), 7.82-7.89 9m, 1H), 7.67 (s, 1H), 7.40-7.48 (m, 2H), 7.25-7.30 (m, 1H), 7.02-7.10 (m, 2H), 6.86-6.89 (m, 1H), 6.60-6.68 (m, 1H), 4.26-4.27 (d, 2H), 3.78 (s, 3H); MS m/z: 347 (M+H$^+$)

20        Compound (33): $^1$H NMR (CDCl$_3$) δ (ppm) 8.45-8.52 (m, 1H), 8.04-8.09 (m, 2H), 7.81-7.98 (m, 4H), 6.22-6.27 (m, 1H), 3.35-3.68 (m, 6H), 2.95 (s, 3H), 2.37-2.43 (m, 2H), 1.90-2.02 (m, 4H); MS m/z: 441(M+H$^+$)

Compound (34): $^1$H NMR(CDCl$_3$) δ (ppm) 8.40 (s, 1H), 8.10-8.16 (m, 1H), 8.03-8.06 (m,
25        1H), 7.50-7.55 (m, 2H), 6.65-6.71 (m, 1H), 6.40-6.48 (m, 1H), 5.90-5.92 (m, 2H), 3.32-3.58 (m, 6H), 2.27-2.35 (m, 2H), 1.84-1.92 (m, 4H); MS m/z: 407 (M+H$^+$)

Compound (35): $^1$H NMR(methanol-$d_4$) δ (ppm) 8.27-8.34 (m, 4H), 8.01-8.13 (m, 2H), 7.52-7.67 (m, 1H), 3.30-3.49 (m, 6H), 2.20-2.28 (m, 6H), 2.17-2.26 (m, 2H), 1.78-1.93 (m,
30        4H); MS m/z: 431 (M+H$^+$)

Compound (36): MS m/z: 393 (M+H⁺)

Compound (37): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.11 (s, 1H), 8.28-8.39 (m, 2H), 8.12 (s, 1H), 7.87-7.91 (m, 1H), 7.25-7.68 (m, 6H), 6.93-7.02 (m, 3H), 6.02 (s, 2H); MS m/z: 437 (M+H⁺)

Compound (38): MS m/z: 423 (M+H⁺)

Compound (39): MS m/z: 365 (M+H⁺)

Compound (40): ¹H NMR (DMSO-$d_6$) δ (ppm) 14.38-14.39 (d, 1H), 12.59 (s, 1H), 7.65-7.75 (m, 3H), 7.31-7.45 (m, 3H), 6.45-6.76 (m, 3H), 5.95 (s, 2H), 4.14 (s, 2H);     MS m/z: 361 (M+H⁺)

Compound (41): ¹H NMR (DMSO-$d_6$) δ (ppm) 9.04-9.08 (s, 1H), 8.46-8.49 (m, 1H), 8.14-8.22 (m, 2H), 7.78-7.81 (m, 1H), 7.34-7.40 (m, 1H), 4.18 (m, 1H), 2.32-2.36 (m, 6H), 2.16-2.22 (m, 1H), 1.98-2.06 (m, 4H), 1.55-1.80 (m, 2H); MS m/z: 336 (M+H⁺)

Compound (42): MS m/z: 407 (M+H⁺)

Compound (43): ¹H NMR(methanol-$d_4$) δ (ppm) 9.21 (s, 1H), 7.98-8.07 (m, 2H), 8.45-8.52 (m, 2H), 7.40-7.48 (m, 1H), 6.63-6.72 (m, 1H), 3.35-3.52 (m, 6H), 2,18-2.25 (m, 2H), 1.80-1.92 (m, 4H); MS m/z: 364 (M+H⁺)

Compound (44): ¹H NMR (methanol-$d_4$) δ (ppm) 8.15-8.22 (m, 3H), 7.96-7.99 (m, 1H), 7.58-7.63 (m, 2H), 6.91-6.98 (m, 1H), 4.08 (s, 1H), 2.71-2.79 (m, 2H), 2.21-2.43 (m, 8H), 1.78-2.00 (m, 2H); MS m/z: 403(M+H⁺)

Compound (45):  MS m/z: 431 (M+H⁺)

Compound (46): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 14.84 (s, 1H), 10.98 (s, 1H), 8.30-8.62 (m, 3H), 8.07 (s, 1H), 7.50-7.75 (m, 4H), 7.00-7.16 (m, 2H), 6.26 (s, 2H), 3.25 (s, 3H); MS m/z: 436 (M+H$^+$)

Compound (47): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 15.20 (s, 1H), 11.22 (s, 1H), 8.42-8.58 (m, 5H), 8.10-8.14 (m, 1H), 7.85-7.96 (m, 2H), 7.55-7.70 (m, 2H), 7.12-7.17 (m, 1H), 3.24 (s, 3H); MS m/z: 460 (M+H$^+$)

Compound (48): ${}^1$H NMR (methanol-$d_4$) δ (ppm) 9.32 ( s, 1H), 8.52-8.64 (m, 2H), 8.26-8.29 (m, 1H), 8.11-8.16 (m, 1H), 7.59-7.66 (m, 1H), 6.70-6.78 (m, 1H), 3.68-3.76 (m, 2H), 2.90-3.00 (m, 6H), 1.92-2.08 (m, 6H); MS m/z: 350(M+H$^+$)

Compound (49): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 8.35-8.50 (m, 3H), 8.11-8.15 (m, 1H), 7.48-7.74 (m, 5H), 7.00-7.14 (m, 2H), 3.89 (s, 3H), 3.23 (s, 3H); MS m/z: 422 (M+H$^+$)

Compound (50): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 8.75 (s, 1H), 8.27-8.30 (m, 1H), 8.16-8.18 (m, 1H), 7.46-7.64 (m, 2H), 7.41-7.43 (m, 1H), 7.00-7.07 (m, 2H), 6.87-6.93 (m, 2H), 6.71-6.75 (m, 1H), 6.00 (s, 2H), 4.65-4.67 (d, 2H), 3.81 (s, 3H); MS m/z: 402 (M+H$^+$)

Compound (51): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 8.68 (s, 1H), 8.27 –8.29 (m, 1H), 8.17-8.19 (m, 1H), 7.17-7.18 (d, 2H), 7.00-7.01 (s, 1H), 6.90-6.94 (m, 2H), 6.71-6.75 (m, 1H), 6.55 (s, 1H), 6.00 (s, 2H), 4.64-4.66 (d, 2H), 3.79 (s, 6H); MS m/z: 432 (M+H$^+$)

Compound (52): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 8.87 (s, 1H), 8.10-8.25 (m, 5H), 7.50-7.60 (m, 1H), 6.70-6.95 (m, 4H), 6.00 (s, 2H), 4.68-4.71 (d, 2H); MS m/z: 424 (M+H$^+$)

Compound (53): ${}^1$H NMR (DMSO-$d_6$) δ (ppm) 14.80 (s, br, 1H), 9.10 (s, br, 1H), 8.31-8.38 (m, 2H), 7.35-7.85 (m, 4H), 6.70-6.95 (m, 3H), 6.00 (s, 2H), 4.65-4.70 (d, 2H); MS m/z: 390 (M+H$^+$)

<u>Compound (54)</u>: $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.80 (s, 1H), 8.15-8.38 (m, 4H), 7.70-7.85 (m, 2H), 7.00 (s, 1H), 6.85-6.90 (m, 2H), 6.72-6.78 (m, 1H), 6.00 (s, 2H), 4.65-4.67 (d, 2H); MS m/z: 440 (M+H$^+$)

5     <u>Compound (55)</u>: $^1$H NMR (DMSO-$d_6$) 14.85 (s, br, 1H), 8.80 (s, br, 1H), 8.15-8.25 (m, 4H), 7.85-7.92 (m, 2H), 7.00 (s, 1H), 7.11 (s, 2H), 6.68-6.72 (m, 1H), 6.00 (s, 2H), 4.65-4.68 (d, 2H); MS m/z: 440 (M+H$^+$)

<u>Compound (56)</u>: $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.71 (s, 1H), 8.65 (s, 1H), 8.48-8.59 (m,

10     1H), 8.10-8.30 (m, 2H), 7.78-7.82 (m, 1H), 7.50-7.65 (m, 2H), 7.30-7.45 (m, 2H), 7.02-7.08 (m, 1H), 6,70-6.80 (m, 1H), 4.80-4.82 (m, 2H), 3.82 (s, 3H); MS m/z: 359 (M+H$^+$)

<u>Compound (57)</u>: $^1$H NMR (DMSO-$d_6$) δ14.78 (s, br, 1H), 8.85 (s, br, 1H), 8.60 (s, 1H), 8.50 (d, 1H), 8.05-8.30 (m, 3H), 7.75-7.80 (m, 1H), 7.50-7.60 (m, 1H), 7.30-7.40(m, 1H),

15     6.72-6.80 (m, 1H), 4.75-4.82 (d, 2H); MS m/z: 381 (M+H$^+$)

<u>Compound (58)</u>: $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.76 (s, 1H), 8,88 (s, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 8.19-8.26 (m, 3H), 7.72-7.94 (m, 3H), 7.50-7.55 (m, 2H), 6.75-6.80 (m, 1H), 4.82-4.84 (d, 2H); MS m/z: 347 (M+H$^+$)

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<u>Compound (59)</u>: $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.90 (s, 1H), 8.91 (s, 1H), 8.68 (s, 1H), 8.45-8.48 (d, 1H), 8.15-8.30 (m, 4H), 7.72-7.95 (m, 3H), 7.35-7.40 (m, 1H), 6.70-6.79 (m, 1H), 4.80-4.85 (d, 2H); MS m/z: 397 (M+H$^+$)

25     <u>Compound (60)</u>: $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.72 (s, 1H), 8.66 (s, 1H), 8.47-8.48 (m, 1H), 8.17-8.31 (m, 2H), 7.81-7.83 (d, 1H), 7.35-7.39 (m, 1H), 7.20-7.21 (d, 2H), 6.63-6.78 (m, 2H), 4.80-4.82 (m, 2H), 3.80 (s, 6H); MS m/z: 389 (M+H$^+$)

<u>Compound (61)</u>: $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.50 (s, 1H), 8.65-8.66 (m, 1H), 8.47-8.49

30     (m, 1H), 8.16-8.18 (m, 1H), 7.80-7.83 (m, 1H), 7.61-7.65 (m, 2H), 7.35-7.40 (m, 1H),

7.10-7.12 (d, 1H), 6.73-6.77 (m, 1H), 4.79-4.81 (d, 2H), 3.81-3.83 (d, 2H); MS m/z: 389 (M+H⁺)

Compound (62): ¹H NMR (DMSO-$d_6$) δ (ppm) 14.90 (s, 1H), 8.91 (s, 1H), 8.66 (s, 1H),

5   8.02-8.35 (m, 6H), 7.81-7.84 (m, 1H), 7.32-7.39 (m 1H), 6.75-6.80 (m, 1H), 4.82-4.84 (d, 2H), 3.28-3.33 (d, 3H); MS m/z: 407 (M+H⁺)

Compound (63): ¹H NMR (DMSO-$d_6$) 14.50 (s, 1H), 8.17-8.57 (m, 3H), 7.57-7.64 (m, 2H), 7.10 (s, 1H), 6.41-6.61 (m, 4H), 4.74-4.75 (d, 2H), 3.75-3.87 (m, 12 H); MS m/z: 448

10  (M+H⁺)

Compound (64): ¹H NMR (DMSO-$d_6$) 8.11-8.42 (m, 7H), 7.85-7.90 (m, 1H), 6.55-6.60 (m, 1H), 6.38-6.40 (m, 1H), 4.78-4.81 (d, 2H), 3.72-3.74 (m, 9H); MS m/z: 466 (M+H⁺)

15  Compound (65): ¹H NMR (DMSO-$d_6$) δ (ppm) 8.34-8.58 (m, 2H), 7.70-7.73 (m, 2H), 7.13-7.23 (m, 1H), 6.85-7.10 (m, 4H), 6.19 (s, 1H), 3.74-3.88 (m, 9H); MS m/z: 404 (M+H⁺)

Compound (66): ¹H NMR (DMSO-$d_6$) δ (ppm) 8.50-8.58 (m, 3H), 8.32-8.36 (m, 1H),

20  8.24-8.27 (m 1H), 7.78-7.96 (m, 2H), 6.79-6.84 (m, 1H), 3.75-3.79 (m, 2H), 3.15-3.23 (m, 6H), 1.91-2.12 (m, 6H); MS m/z: 417(M+H⁺)

Compound (67): ¹H NMR (DMSO-$d_6$)δ 8.49 (m, 1H), 8.29-8.33 (m, 1H), 8.15-8.22 (m, 1H), 7.81-7.88 (m, 2H), 7.45-7.55 (m, 1H), 7.10-7.14 (m, 1H), 6.72-6.78 (m, 1H), 3.91 (s,

25  3H), 3.72-3.79 (m, 2H), 3.05-3.24 (m, 6H), 1.97-2.08 (m, 6H); MS m/z: 377(M+H⁺)

Compound (68): ¹H NMR (methanol-$d_4$) δ (ppm) 8.14-8.18 (m, 1H), 7.95-7.97 (m, 1H), 7.45-7.50 (m, 1H), 7.51 (s, 1H), 6.82-6.86 (m, 1H), 6.55-6.59 (m, 1H), 5.93 (s, 2H), 3.40- 3.54 (m, 2H), 2.52-2.68 (m, 6H), 1.68-1.95 (m, 6H); MS m/z: 393(M+H⁺)

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Compound (69): ¹H NMR (methanol-$d_4$) δ (ppm) 8.25-8.28 (m, 1H), 8.05-8.08 (m,1H), 7.20-7.24 (m, 2H), 6.57-6.73 (m, 2H), 3.91 (s, 6H), 3.55-3.63 (m, 2H), 2.74-2.93 (m, 6H), 1.82-2.08 (m, 6H); m/z: 409(M+H⁺)

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Compound (70): ¹H NMR (methanol-$d_4$) δ (ppm) 8.44-8.48 (m, 1H), 8.04-8.10 (m, 1H), 7.63-7.69 (m, 2H), 7.45-7.52 (m, 1H), 6.98-6.12 (m, 2H), 4.32 (s, 1H), 3.88 (s, 3H), 2.82-2.91 (m, 2H), 2.64-2.68 (m, 4H), 2.38-2.46 (m, 4H), 1.95-2.15 (m, 2H); MS m/z: 365(M+H⁺)

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Compound (71): ¹H NMR (DMSO-$d_6$) δ (ppm) 11.27 (s, 1H), 8.50-8.54 (m, 1H), 8.34-8.37 (m, 2H), 8.00-8.06 (m, 1H), 7.78-7.87 (m, 2H), 7.42-7.60 (m, 3H), 7.38 (s, 2H), 6,99-7.13 (m, 2H), 3.89 (s, 3H); MS m/z: 423 (M+H⁺)

Compound (72): ¹H NMR (DMSO-$d_6$) δ (ppm) 15.30 (s, 1H), 11.18 (s, 1H), 8.38-8.51 (m, 15    5H), 7.82-7.98 (m, 3H), 7.30-7.58 (m, 4H), 7.00-7.07 (m, 1H); MS m/z: 461(M+H⁺)

Compound (73): ¹H NMR (DMSO-$d_6$) δ (ppm) 9.35 (s, 1H), 8.68-8.71 (m, 1H), 8.40-8.47 (m, 2H), 8.30-8.33 (m, 1H), 7.59-7.66 (m, 1H), 7.11 (s, 2H), 6.93-6.99 9m, 1H), 6.22 (s, 1H), 3.79 (s, 6H); MS m/z: 375(M+H⁺)

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Compound (74): ¹H NMR (DMSO-$d_6$) δ (ppm) 14.98 (s, br, 1H), 11.92 (s, br, 1H), 8.60 (s, 1H), 8.10-8.24 (m, 2H), 7.45-7.58 (m, 3H), 7.08-7.13 (m, 1H), 6.82-6.88 (m, 1H), 6.65-6.70 (m, 1H), 5.93 (s, 2H), 3.84-3.88 (m, 2H), 2.85-2.91 (m, 2H); MS m/z: 376(M+H⁺)

25    Compound (75): ¹H NMR (DMSO-$d_6$) δ (ppm) 14.40 (s, br, 1H), 1.57 (s, br, 1H), 8.55 (s, 1H), 8.15-8.22 (m, 2H), 7.42-7.65 (m, 4H), 7.07-7.10 (m, 1H), 6.66-6.68 (m, 1H), 6.65-6.74 (m, 1H), 3.92 (s, 3H), 3.78-3.86 (m, 1H), 2.85-2.92 (m, 2H); MS m/z: 362(M+H⁺)

Compound (76): MS m/z: 397 (M+H⁺)

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Compound (77): MS m/z: 396 (M+H$^+$)

Compound (78): MS m/z: 396 (M+H$^+$)

5       Compound (79): MS m/z: 433 (M+H$^+$)

Compound (80): MS m/z: 388 (M+H$^+$)

Compound (81): MS m/z: 388 (M+H$^+$)

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Compound (82): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.47-8.49 (m, 2H), 8.22-8.25 (m, 1H), 7.95-7.98 (m, 1H), 7.25-7.34 (m, 4H), 6.60-6.95 (m, 5H), 6.56-6.60 (d, 2H), 4.14-4.22 (d, 2H), 3.68-3.72 (m, 3H); MS m/z: 373 (M+H$^+$)

15      Compound (83): MS m/z: 408 (M+H$^+$)

Compound (84): MS m/z: 439 (M+H$^+$)

Compound (85): MS m/z: 423 (M+H$^+$)

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Compound (86): MS m/z: 377 (M+H$^+$)

Compound (87): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.38 (s, 1H), 10.79 (s, 1H), 8.27-8.37 (m, 2H), 7.23-7.28 (m, 1H), 6.82-7.00 (m, 6H), 6.14-6.16 (m, 1H), 4.19 (s, 1H), 3.70-3.74 (m, 25     9H); MS m/z: 418 (M+H$^+$)

Compound (88): MS m/z: 410 (M+H$^+$)

Compound (89): MS m/z: 404 (M+H$^+$)

30

Compound (90): MS m/z: 391 (M+H$^+$)

Compound (91): MS m/z: 422 (M+H$^+$)

Compound (92): MS m/z: 377 (M+H$^+$)

5      Compound (93): MS m/z: 417 (M+H$^+$)

Compound (94): MS m/z: 408 (M+H$^+$)

Compound (95): MS m/z: 394 (M+H$^+$)

10

Compound (96): MS m/z: 394 (M+H$^+$)

Compound (97): MS m/z: 437 (M+H$^+$)

15      Compound (98): MS m/z: 451 (M+H$^+$)

Compound (99): MS m/z: 380 (M+H$^+$)

Compound (100): $^1$H NMR(CDCl$_3$) δ (ppm) 12,35 (s, 1H), 8.02-8.20 (m, 3H), 7.10-7.18
20      (m, 1H), 6.65-6.80 (m, 3H), 6.45-6.52 (m, 1H), 4.07-4.08 (d 2H), 3.72 (s, 3H), 3.42-3.52
(m, 2H), 3.25-3.38 (m, 4H), 2.15-2.22 (m, 2H), 1.80-1.90 (m, 4H); MS m/z: 407(M+H$^+$)

Compound (101): $^1$H NMR(CDCl$_3$) δ (ppm) 7.70-7.75 (m, 1H), 7.39 9s, 2H), 7.02-7.25
(m, 2H), 6.55-6.68 (m, 5H), 4.25 (s, 2H), 3.96 9s, 2H), 3.54 (s, 3H); MS m/z: 361 (M+H$^+$)

25

Compound (102): MS m/z: 431 (M+H$^+$)

Compound (103): MS m/z: 466 (M+H$^+$)

30      Compound (104): MS m/z: 467 (M+H$^+$)

93

Compound (**105**): MS m/z: 392 (M+H$^+$)

Compound (**106**): MS m/z: 437 (M+H$^+$)

5        Compound (**107**): MS m/z: 409 (M+H$^+$)

Compound (**108**): MS m/z: 403 (M+H$^+$)

Compound (**109**): MS m/z: 452 (M+H$^+$)

10

Compound (**110**): MS m/z: 448 (M+H$^+$)

Compound (**111**): MS m/z: 406 (M+H$^+$)

15        Compound (**112**): MS m/z: 453 (M+H$^+$)

Compound (**113**): MS m/z: 488 (M+H$^+$)

Compound (**114**): *See* Example 6

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Compound (**115**): $^1$H NMR (DMSO-$d_6$) δ (ppm) 11.40 (s, 1H), 10.0 (s, 1H), 8.40-8.43 (m, 1H), 8.01-8.04 (m, 1H), 7.01-7.06 (m, 2H), 6.81-6.95 (m, 4H), 6.23-6.25 (t, 1H), 3.80 (s, 6H); MS m/z: 426 (M+H$^+$). Calculated for C$_{21}$H$_{17}$F$_2$N$_5$O$_3$: 425.13

25        Compound (**116**): $^1$H NMR (DMSO-$d_6$) δ (ppm) 11.34 (s, 1H), 10.02 (s, 1H), 8.43-8.45 (m, 1H), 8.06-8.16 (m, 2H), 7.87-7.90 (m, 1H), 7.64-7.70 (t, 1H), 7.43-7.46 (d, 1H), 7.05-7.10 (m, 3H), 6.25-6.27 (t, 1H), 3.81 (s, 6H); MS m/z: 458 (M+H$^+$). Calculated for C$_{22}$H$_{18}$F$_3$N$_5$O$_3$: 457.13

Compound (117): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.93 (s, 1H), 10.07 (s, 1H), 8.41-8.44 (m, 1H), 8.04-8.08 (m, 1H), 7.04-7.54 (m, 11H), 6.74-6.77 (m, 1H), 6.24-6.26 (t, 1H), 5.16 (s, 2H), 3.80-3.84 (d, 6H); MS m/z: 496 (M+H$^+$). Calculated for $C_{22}H_{19}F_3N_5O_5$: 495.19

5      Compound (118): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.76 (s, 1H), 10.07 (s, 1H), 8.40-8.43 (m, 1H), 8.02-8.05 (m, 1H), 7.33-7.34 (d, 1H), 6.94-7.11 (m, 5H), 6.24-6.26 (t, 1H), 6.05 (s, 2H), 3.77-3.80 (d, 6H); MS m/z: 434 (M+H$^+$). Calculated for $C_{22}H_{19}N_5O_5$: 433.14

Compound (119): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.68 (s, 1H), 10.04 (s, 1H), 8.40-8.42-t,
10     1H), 8.03-8.06 (t, 1H), 7.35-7.36 (d, 1H), 7.00-7.19 (m, 5H), 6.25 (s, 1H), 3.78-3.82 (m, 12H); MS m/z: 450 (M+H$^+$). Calculated for $C_{23}H_{23}N_5O_5$: 449.17

Compound (120): $^1$H NMR (DMSO-$d_6$) δ10.86 (s, 1H), 10.05 (s, 1H), 8..35-8.37 (m, 1H), 8.00-8.02 (m, 1H), 7.65-7.68 (d, 2H), 7,34-7.40 (t, 2H), 6.96-7.12 (m, 8H), 6.19-6.20 (t,
15     1H), 3.72-3.76 (d, 6H); MS m/z: 482 (M+H$^+$). Calculated for $C_{27}H_{21}N_5O_4$: 481.18

Compound (121): $^1$H NMR (DMSO-$d_6$) δ11.05 (s, 1H), 8.28-8.30 (s, 1H), 8.11-8.16 (t, 1H), 7.92-7.96 (m, 1H), 7.73-7.76 (d, 2H), 7.17-7.29 (m, 1H), 7.00 (s, 1H), 6.91 (s, 2H), 6.80-6.84 (m, 1H), 6.02 (s, 2H), 4.70-4.72 (d, 2H); MS m/z: 471 (M+H$^+$). Calculated for
20     $C_{27}H_{17}F_3N_4O_4$: 470.12

Compound (122): $^1$H NMR (DMSO-$d_6$) δ (ppm) 11.22 (s, 1H), 8.28-8.31 (m, 1H), 8.15 (s, 2H), 7.91-7.95 (m, 1H), 7.81-7.84 (d, 1H), 7.64-7.67 (t, 1H), 7.40-7.42 (d, 1H), 6.80-7.00 (m, 4H), 6.02 (s, 2H), 4.71-4.73 (d, 2H); MS m/z: 456 (M+H$^+$). Calculated for
25     $C_{23}H_{17}F_3N_4O_3$: 455.12

Compound (123): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.83 (s, 1H), 8.27-8.30 (m, 1H), 8.12-8.16 (m, 1H), 7.90-7.94 (m, 1H), 7.17-7.52 (m, 9H), 7.00 (s, 1H), 6.90 (d, 3H), 6.71-6.84 (m, 2H), 6.02 (s, 1H), 5.14 (s, 1H), 4.71-4.73 (d, 2H); MS m/z: 494 (M+H$^+$). Calculated
30     for $C_{29}H_{24}N_4O_4$: 492.18

Compound (124): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.81 (s, 1H), 8.27-8.29 (m, 1H), 8.13-8.17 (t, 1H), 7.92-7.95 (m, 1H), 7.66-7.69 (m, 2H), 7.38-7.43 (t, 2H), 6.79-7.16 (m, 9H), 6.02 (s, 2H), 4.70-4.72 (m, 2H); MS m/z: 480(M+H$^+$). Calculated for $C_{27}H_{21}N_5O_4$: 479.16

Compound (125): $^1$H NMR (DMSO-$d_6$) δ10.60 (s, 1H), 8.26-8.29 (m, 1H), 8.15-8.17 (t, 1H), 7.89-7.93 (m, 1H), 7.38-7.39 (d, 1H), 6.79-7.12 (m, 6H), 6.02 (s, 2H), 4.70-4.72 (d, 2H), 3.76-3.80 (d, 6H); MS m/z: 448(M+H$^+$). Calculated for $C_{23}H_{21}N_5O_5$: 447.15

Compound (126): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.62 (s, 1H), 8.23-8.25 (m, 1H), 8.09 (t, 1H), 7.84-7.88 (m, 1H), 7.27-7.28 (d, 1H), 6.75-7.03 (m, 6H), 5.99-6.00 9d, 2H), 4.66-4.68 (d, 2H); MS m/z: 432(M+H$^+$). Calculated for $C_{22}H_{17}N_5O_5$: 431.12

Compound (127): $^1$H NMR (DMSO-$d_6$) δ (ppm) 11.03 (s, 1H), 8.24-8.26 (m, 1H), 8.13-8.17 (t, 1H), 7.90-7.93 (m, 1H), 7.70-7.73 (d, 2H), 7.78-7.40 (d, 2H), 6.78-6.82 (m, 1H), 6.40-6.54 (d, 2H), 6.54-6.55 (d, 1H), 6.40 (s, 1H), 4.71-4.73 (d, 2H), 3.72 (s, 6H); MS m/z: 488(M+H$^+$). Calculated for $C_{23}H_{20}F_3N_5O_4$: 487.15

Compound (128): $^1$H NMR (DMSO-$d_6$) δ11.20 (s, 1H), 8.11-8.27 (m, 3H), 7.90-7.93 (m, 1H), 7.79-7.82 (d, 1H), 7.58-7.64 (t, 1H), 7.37-7.39 (d, 1H), 6.77-6.82 (m, 1H), 6.40-6.54 (d, 2H), 6.39-6.40 (d, 1H), 4.71-4.73 (d, 2H), 3.72 (s, 6H); MS m/z: 472(M+H$^+$). Calculated for $C_{23}H_{20}F_3N_5O_3$: 471.15

Compound (129): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.80 (s, 1H), 8.14-8.25 (m, 2H), 7.90-7.93 (m, 1H), 7.62-7.90 (m, 2H), 6.77-7.40 (m, 7H), 6.54-6.55 (d, 2H), 6.39-6.40 (t, 2H), 3.71 (s, 6H); MS m/z: 496(M+H$^+$). Calculated for $C_{28}H_{25}F_3N_5O_4$: 495.19

Compound (130): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.80 (s, 1H), 8.15-8.25 (m, 2H), 7.88-7.91 (d, 1H), 7.07-7.48 (m, 9H), 6.40-6.81 (m, 5H), 5.11 (s, 2H), 4.71-4.73 (d, 2H), 3.71 (s, 6H); MS m/z: 510(M+H$^+$). Calculated for $C_{29}H_{27}F_3N_5O_4$: 509.21

Compound (131): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.64 (s, 1H), 8.12-8.24 (m, 2H), 7.86-7.89 (m, 1H), 7.28-7.29 (d, 1H), 6.76-7.04 (m, 3H), 6.54-6.55 (d, 2H), 6.39-6.41 (t, 1H), 6.00 (s, 2H), 4.70-4.72 (d, 2H), 3.72 (s, 6H); MS m/z: 448(M+H⁺). Calculated for $C_{23}H_{21}F_3N_5O_5$: 447.15

Compound (132): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.57 (s, 1H), 8.15-8.24 (m, 2H), 7.87-7.90 (m, 1H), 7.35-7.36 (m, 1H), 7.06-7.10 (m, 1H), 6.94-6.97 (d, 1H), 6.76-6.81 (m, 1H), 6.54-6.55 (d, 2H), 6.39-6.40 (t, 1H), 4.71-4.73 (d, 2H), 3.72-3.77 (m, 12H); MS m/z: 464 (M+H⁺). Calculated for $C_{24}H_{25}F_3N_5O_5$: 463.19

Compound (133): ¹H NMR (DMSO-$d_6$) δ (ppm) 11.05 (s, 1H), 8.14-8.26 (m, 2H), 7.89-7.92 (d, 1H), 7.37-7.57 (m, 3H), 7.07-7.10 (d, 1H), 6.80-6.88 (m, 2H), 6.54 (s, 2H), 6.40 (s, 1H), 3.72 (s, 6H); MS m/z: 422 (M+H⁺). Calculated for $C_{22}H_{20}FN_5O_3$: 421.42

Compound (134): ¹H NMR (DMSO-$d_6$) δ (ppm) 11.25 (s, 1H), 8.13-8.27 (m, 2H), 7.72-7.94 (m, 5H), 6.80-6.82 (m, 1H), 6.54-6.55 (d, 2H), 6.40-6.41 (t, 1H), 4.71-4.73 (d, 2H), 3.72 (s, 6H); MS m/z: 472 (M+H⁺). Calculated for $C_{23}H_{20}F_3N_5O_3$: 471.15

Compound (135): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.62 (s, 1H), 8.14-8.25 (m, 2H), 7.87-7.90 (m, 1H), 7.52 (s, 1H), 7.06-7.35 (m, 3H), 6.76-6.80 (m, 1H), 6.54-6.55 (d, 2H), 6.40 (s, 1H), 4.70-4.72 (d, 2H), 3.72 (s, 6H), 2.78-2.88 (m, 4H), 1.96-2.06 (m, 2H); MS m/z: 444 (M+H⁺). Calculated for $C_{25}H_{25}F_3N_5O_3$: 443.20

Compound (136): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.29 (s, 1H), 8.23-8.25 (m, 1H), 8.14-8.18 (t, 1H), 7.88-7.91 (m, 1H), 7.07-7.33 (m, 3H), 6.77-6.81 (m, 1H), 6.54-6.62 (m, 3H), 6.39 (s, 1H), 4.71-4.73 (d, 2H), 3.71-3.76 (d, 9H) ; MS m/z: 420(M+H⁺). Calculated for $C_{22}H_{21}N_5O_4$: 419.16

Compound (137): ¹H NMR (DMSO-$d_6$) δ (ppm) 8.61 (s, 1H), 8.45-8.46 (d, 1H), 8.22-8.30 (m, 2H), 7.89-7.91 (m, 1H), 7.76-7.79 (m, 1H), 7.13-7.36 (m, 4H), 6.72-6.83 (m, 1H),

6.59-6.61 (m, 1H), 4.82-4.84 (d. 2H), 3.76 (s. 3H); MS m/z: 375(M+H$^+$). Calculated for C$_{20}$H$_{18}$N$_6$O$_2$: 374.40

Compound (138): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.60 (s, 1H), 8.10-8.15 (m, 1H), 7.88-7.92 (t, 1H), 7.61-7.70 (m, 1H), 6.41-7.14 (m, 8H), 5.85 (s, 2H), 4.49-4.51 (d, 2H), 3.62 (s, 3H); MS m/z: 418(M+H$^+$). Calculated for C$_{22}$H$_{19}$N$_5$O$_4$: 417.14

Compound (139): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.95 (s, 1H), 9.94 (s, 1H), 8.42-8.44 (m, 1H), 8.06-8.11 (m, 1H), 7.62-7.63 (d, 1H), 6.91-7.14 (m, 5H), 6.31-6.33 (t, 1H), 6.12 (s, 2H), 3.86 (s, 6H); MS m/z: 434 (M+H$^+$). Calculated for C$_{22}$H$_{19}$N$_5$O$_5$: 433.14

Compound (140): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.89 (s, 1H), 10.20 (s, 1H), 8.33-8.38 (m, 1H), 8.01-8.04 (m, 1H), 7.22-7.33 (m, 2H), 7.10-7.22 (m, 1H), 7.01-7.09 (m, 3H), 6.62-6.69 (m, 1H), 6.21-6.25 (m, 1H), 3.78-3.87 (m, 9H); MS m/z: 420 (M+H$^+$) Calculated for C$_{22}$H$_{21}$N$_5$O$_4$: 419.43

Compound (141): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.90 (s, 1H), 9.91 (s, 1H), 8.38-8.42 (m, 1H), 7.98-8.02 (m, 1H), 7.57-7.70 (m, 1H), 6.94-7.38 (m, 6H), 6.66-6.70 (m, 1H), 6.03 (s, 2H), 3.83 (s, 3H); MS m/z: 404 (M+H$^+$). Calculated for C$_{21}$H$_{17}$N$_5$O$_4$: 403.13

Compound (142): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.30 (s, 1H), 8.23-8.25 (m, 1H), 8.14-8.18 ( t, 1H), 7.07-7.33 (m, 3H), 6.62-6.81 (m, 1H), 6.40-6.59 (m, 3H), 6.39-6.40 (t, 1H), 4.71-4.73 (m, 2H), 3.67-3.76 (m, 9H); MS m/z: 434 (M+H$^+$). Calculated for C$_{23}$H$_{23}$N$_5$O$_4$: 433.18

Compound (143): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.61 (s, 1H), 8.45-8.46 (d, 1H), 8.23-8.30 (m, 2H), 7.89-7.91 (m, 1H), 7.76-7.79 (m, 1H), 7.13-7.34 (m, 4H), 6.78-6.82 (m, 1H), 6.59-6.61 (d, 1H), 4.82-4.84 (d, 2H), 3.76 (s, 3H); MS m/z: 375 (M+H$^+$). Calculated for C$_{20}$H$_{18}$N$_6$O$_2$: 374.15

Compound (144): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.62 (s, 1H), 8.42-8.45 (t, 1H), 88.10-8.23 (m, 2H), 7.76-7.79 (d, 1H), 7.60-7.62 (m, 1H), 7.23-7.37 (m, 2H), 6.78-6.87 (m, 3H), 6.12-6.18 (m, 1H), 4.82-4.84 (d, 2H), 3.78 (s, 6H); MS m/z: 405 (M+H$^+$). Calculated for $C_{21}H_{20}N_6O_3$: 404.16

5

Compound (145): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.76 (s, 1H), 8.22-8.25 (m, 1H), 8.13-8.17 (t, 1H), 7.87-7.90 (m, 1H), 7.06-7.09 (d, 1H), 6.77-6.86 (m, 3H), 6.53-6.54 (d, 2H), 6.38-6.40 (t, 1H), 6.19-6.21 (t, 1H), 4.71-4.73 (d, 2H), 3.68-3.78 (m, 12H); MS m/z: 464 (M+H$^+$). Calculated for $C_{24}H_{25}N_5O_5$: 463.19

10

Compound (146): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.60 (s, 1H), 8.51-8.53 (d, 2H), 8.00-8.01 (t, 1H), 7.62-7.64 (d, 1H), 7.24-7.37 9m, 3H), 6.88-6.89 (d, 2H), 6.68-6.78 (m, 2H), 6.20 (s, 1H), 4.66-4.68 (d, 2H), 3.76 (s, 3H); MS m/z: 448 (M+H$^+$). Calculated for $C_{23}H_{21}N_5O_5$: 447.15

15

Compound (147): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.62 (s, 1H), 8.46-8.47 9d, 1H), 8.23-8.29 (m, 2H), 7.68-7.92 (m, 6H), 7.34-7.38 (t, 1H), 6.78-6.82 (t, 1H), 4.82-4.84 9d, 2H); MS m/z: 413 (M+H$^+$). Calculated for $C_{20}H_{15}F_3N_5O$: 412.13

20　Compound (148): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.69 (br, s, 1H), 8.61-8.62 (d, 1H), 8.45-8.47 9m, 1H), 8.21-8.28 (m, 2H), 7.86-7.89 (m, 1H), 7.76-7.79 (d, 1H), 7.31-7.38 (m, 2H), 7.02-7.06 (m, 1H), 6.89-6.92 (m, 1H), 6.77-6.81 (m, 1H), 6.00 (s, 2H), 4.81-4.83 (d, 2H); MS m/z: 389 (M+H$^+$). Calculated for $C_{20}H_{16}N_6O_3$: 388.13

25　Compound (149): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.61 (s, 1H), 8.45-8.47 (m, 1H), 8.21-8.30 9m, 2H), 7.90-7.92 (m, 1H), 7.76-7.79 (m, 1H), 7.63-7.67 (m, 2H), 7.33-7.40 (m, 3H), 6.96-7.12 (m, 4H), 6.78-6.82 (m, 1H), 4.81-4.83 (d, 2H); MS m/z: 437 (M+H$^+$). Calculated for $C_{25}H_{20}N_6O_2$: 436.16

Compound (150): ¹H NMR (DMSO-$d_6$) δ (ppm) 8.62 (s, 1H), 8.44-8.46 (m, 1H), 8.21-8.31 (m, 2H), 7.76-7.90 (m, 2H), 7.32-7.40 (m, 2H), 7.06-7.10 (m, 1H), 6.93-6.96 (m, 1H), 6.77-6.93 (m, 1H), 4.81-4.83 (d, 2H), 3.67-3.77 (m, 6H); MS m/z: 405 (M+H⁺). Calculated for $C_{21}H_{20}N_6O_3$: 404.16

Compound (151): ¹H NMR (methanol-$d_4$) δ (ppm) 7.98-8.01 (m, 2H), 6.85-6.98 (m, 5H), 6.55-6.72 (m, 4H), 5.80 (s, 2H), 5.03-5.10 (d, 2H), 4.50 (s, 2H); MS m/z: 419 (M+H⁺)

Compound (152): ¹H NMR (DMSO-$d_6$) δ (ppm) 8.60 (s, 1H), 8.40-8.44 (m, 1H), 8.21-8.29 (m, 2H), 8.05-8.10 (m, 1H), 7.80-7.86 (m, 1H), 7.08-7.19 (m, 4H), 6.77-6.83(m, 1H), 5.50 (s, 2H), 4.80-4.86 (m, 2H); MS m/z: 378 (M+H⁺)

Compound (153): ¹H NMR (CDCl₃) δ (ppm) 8.57-8.60 (d, 2H), 8.10-8.16 (t, 1H), 7.84-7.87 (d, 1H), 7.28-7.32 (m, 3H), 7.02-7.04 (m, 5H), 6.76-6.84 (m, 1H), 6.58-6.64 (m, 1H), 5.32 (s, 2H), 4.82-4.89 (d, 2H); MS m/z: 376 (M+H⁺)

Compound (154): *See* Example 9.

Compound (155): ¹H NMR (DMSO-$d_6$) 11.00 (s, 1H), 9.50 (s, 1H), 8.28-8.32 (m, 2H), 7.10-7.28 (m, 5H), 6.92-6.97 (m, 1H), 6.47-6.50 (m, 1H), 6.17-6.18 (t, 1H), 3.747-3.749 (d, 9H); MS m/z: 419 (M+H⁺). Calculated for $C_{22}H_{22}N_6O_3$: 418.18

Compound (156): ¹H NMR (methanol-$d_4$) δ (ppm) 8.25-8.35 (br s, 1H), 8.19 (s, 1H), 7.41-7.45 (d, 2H), 6.83-6.96 (m, 5H), 6.16 (s, 1H), 3.3-3.80 (m, 9H); MS m/z: 419 (M+H⁺). Calculated for $C_{22}H_{22}N_6O_3$: 418.18

Compound (157): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.30 (s, 1H), 8.32-8.46 (m, 2H), 7.78-7.93 (m, 4H), 7.00-7.77 (m, 3H), 6.25-6.27 (d, 1H, J=0.069), 3.80-3.82 (d, 6H, J=0.033Hz); MS m/z: 414 (M+H⁺). Calculated for $C_{22}H_{19}N_7O_2$: 413.16

Compound (158): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.50 (s, 1H), 9.66 (s, 1H), 9.59 (s, 1H), 8.14-8.32 (m, 2H), 7.48-7.55 9m, 2H), 7.16 (s, 1H), 6.78-7.09 (m, 5H), 6.08 (1H), 3.65 (s, 6H); MS m/z: 389(M+H⁺). Calculated for $C_{22}H_{21}N_5O_2$: 328.14

5       Compound (159): ¹H NMR (CDCl₃) δ (ppm) 10.34 (s, 1H), 8,27-8.29 (m, 2H), 7.77-7.78 (d, 1H, J=0.03Hz), 7.36 (s, 1H), 7.00-7.01 (d, 2H, J=0.03), 6.73-6.82 (m, 2H), 6,45-6.49 (m, 1H), 6.14-6.15 (t, 1H, J=045Hz), 3.77-3.83 (m, 12H); MS m/z: 449 (M+H⁺). Calculated for $C_{23}H_{24}N_6O_4$: 448.19

10      Compound (160): ¹H NMR (CDCl₃) δ (ppm) 10.56 (s, 1H), 8.43-8.50 (m, 2H), 7.45-7.49 (d, 3H), 6.94-6.98 (m, 4H), 6.36-6.38 (m, 1H), 3.98-4.03 (t, 6H), 3.19 (br s, 6H); MS m/z: 432 (M+H⁺). Calculated for $C_{23}H_{25}N_7O_2$: 431.21

Compound (161): ¹H NMR (CDCl₃) δ (ppm) 10.19 (s, 1H), 8.22-8.24 (m, 1H), 8.11 (br s, 15      1H), 6.60-7.39 (m, 10H), 5.91 (s, 2H), 3.81-3.85 (t, 3H); MS m/z: 403 (M+H⁺). Calculated for $C_{21}H_{18}N_6O_3$: 402.41

Compound (162): ¹H NMR (CDCl₃) δ (ppm) 10.07 (s, 1H), 8.09-8.16 (m, 2H), 7.31-7.35 (m, 1H), 7.22-7.30 (m, 3H), 6.88-6.95 (m, 3H), 6,62-6.75 (m, 3H), 5.84-5.86 (d, 2H), 3.78 20      (s, 3H); MS m/z: 403 (M+H⁺). Calculated for $C_{21}H_{18}N_6O_3$: 402.41

Compound (163): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.77 (br s, 1H), 10.18 (s, 1H), 8.30-8.32 (d, 2H, J=0.06Hz), 7.78 (s, 4H), 7.61-7.62 (d, 1H, J=0.021), 1.73-7.16 (t, 1H, J=0.028), 6.94-6.97 (m, 2H), 6.06-6.05 (d, 2H, J=0.036); MS m/z: 398 (M+H⁺). Calculated for 25      $C_{21}H_{15}N_7O_2$: 397.13

Compound (164): ¹H NMR (DMSO-$d_6$) δ (ppm) 10.49 (s, 1H), 8.88 (s, 1H), 8.25-8.40 (m, 2H), 7,95 (s, 1H), 7.64 (s, 1H), 6.91-7.13 (m, 4H), 6.49-6.58 (m, 1H), 6.03-6.06 (d, 2H), 3.69-3.89 (m, 6H); MS m/z: 433 (M+H⁺). Calculated for $C_{22}H_{20}N_6O_4$: 432.15

30

Compound (165): ¹H NMR (methanol-*d₄*) δ (ppm) 8.32 (s, 1H), 8.09 (s, 1H), 7.34 (s, 1H), 6.88-7.00 (m, 1H), 6.70-6.80 (m, 3H), 6.50-6.70 (m, 2H), 5.90 (d, 2H), 3.71-3.89 (m, 6H); MS m/z: 433 (M+H⁺). Calculated for $C_{22}H_{20}N_6O_4$: 432.15

5          Compound (166): ¹H NMR (methanol-*d₄*) δ (ppm) 8.09-8.21 (m, 2H), 7.30-7.38 (m, 1H), 6.95-6.99 (m, 1H), 6.69-6.82 (m, 5H), 6.09 (s, 1H), 5.88 (s, 2H), 3.70-3.74 (m, 6H); MS m/z: 433 (M+H⁺). Calculated for $C_{22}H_{20}N_6O_4$: 432.15

Compound (167): ¹H NMR (DMSO-*d₆*) δ (ppm) 13.28 (s, 1H), 11.07 (s, 1H), 9.27 (s, 1H),
10         8.23-8.34 (m, 2H), 6.79-7.60 (m, 8H), 6.03 (s, 2H), 2.71 (s, 6H); MS m/z: 416 (M+H⁺). Calculated for $C_{22}H_{21}N_7O_2$: 415.18

Compound (168): ¹H NMR (CDCl₃) δ (ppm) 10.41 (s, 1H), 8.19-8.29 (m, 2H), 7.77-7.80 (m, 1H), 7.03-7.04 (d, 3H), 6.72-6.76 (m, 1H), 6.51-6.55 (m, 2H), 6.14-6.16 (m, 1H), 3.64-
15         3.90 (m, 12H); MS m/z: 449 (M+H⁺). Calculated for $C_{23}H_{24}N_6O_4$: 448.19

Compound (169): ¹H NMR (DMSO-*d₆*) δ (ppm) 9.64 (s, 1H), 9.29 (s, 1H), 8.91 (s, 1H), 8.14-8.33 (m, 2H), 6.73-7.28 (m, 7H), 6.44-6.56 (m, 1H), 6.01 (s, 2H), 4.70 (s, 2H), 3.75-3.78 (d, 3H, J=0.078Hz); MS m/z: 417 (M+H⁺). Calculated for $C_{22}H_{20}N_6O_3$: 416.16

20
Compound (170): ¹H NMR (DMSO-*d₆*) δ (ppm) 9.37 (s, 1H), 8.91-9.02 (d, 1H, J=0.33Hz), 8.15-8.36 (m, 3H), 7.45-7.48 (d, 2H), 6.65-6.98 (m, 6H), 6.02 (s, 2H), 4.69 (s, 2H), 3.76 (s, 3H); MS m/z: 417 (M+H⁺). Calculated for $C_{22}H_{20}N_6O_3$: 416.16

25         Compound (171): ¹H NMR (DMSO-*d₆*) δ (ppm) 13.78 (s, 1H), 9.78 (s, 1H), 8.46 (s, 1H), 7.90-7.97 (m, 2H), 7.31-7.48 (m, 4H), 6.50-6.83 (m, 4H), 5.83 (s, 2H), 4.43 (s, 2H); MS m/z: 412 (M+H⁺). Calculated for $C_{22}H_{17}N_7O_2$: 411.14

Compound (172): ¹H NMR (DMSO-*d₆*) δ (ppm) 7.70-7.78 (m, 2H), 7.45 (s, 1H), 7.30-
30         7.35(m, 1H), 7.0-7.06 (m, 2H), 6.60-6.68 (m, 2H), 5.61-6.12 (m, 3H), 560-5.65(m, 1H),

5.06 (s, 2H), 3.77 (s, 2H), 2.93-3.02 (d, 6H); MS m/z: 447 (M+H$^+$). Calculated for C$_{23}$H$_{22}$N$_6$O$_4$: 446.17

Compound (173): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.16-8.19 (m, 1H), 8.01-8.03 (m, 1H), 7.20-7.23 (m, 2H), 6.62-6.84 (m, 6H), 5.87 (s, 2H), 4.58(s, 2H), 2.83-2.86 (m, 6H); MS m/z: 430(M+H$^+$). Calculated for C$_{23}$H$_{23}$N$_7$O$_2$: 429.19

Compound (174): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.02-8.15 (m, 2H), 6.69-6.81 (m, 2H), 6.60-6.67 (m, 4H), 6.04 (s, 1H), 5.45-5.87 (m, 2H), 4.57 (s, 2H), 3.69-3.73 (d, 6H); MS m/z: 447 (M+H$^+$). Calculated for C$_{23}$H$_{22}$N$_6$O$_4$: 446.17

Compound (175): $^1$H NMR (DMSO-$d_6$) δ (ppm) 12.20 (s, 1H), 8.04-8.23 (m, 4H), 8.81-7.90 (m, 1H), 6.82-6.97 (d, 3H), 6.67-6.78 (m, 2H), 6.44-6.48 (d, 1H, J=0.24Hz), 6.01 (s, 2H), 5.55-4.59 (m, 2H), 3.67-3.88 (m, 6H); MS m/z: 447 (M+H$^+$). Calculated for C$_{23}$H$_{22}$N$_6$O$_4$: 446.17

Compound (176): $^1$H NMR (Acetone-d6) δ (ppm) 8.78-8.95 (m, 2H), 8.30-8.60 (m, 2H), 7,95 (s, 1H), 7.65-7.70 (m, 1H), 7.44-7.48 (m, 1H), 7.10-7.38 (m, 3H), 6.91-6.98 (m, 1H), 6.55-6.65 (m, 1H), 3.90 (s, 3H); MS m/z: 399(M+H$^+$). Calculated for C$_{21}$H$_{18}$N$_8$O: 398.16

Compound (177): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.51 (s, 1H), 8.23-8.50 (m, 2H), 7.91-7.94 (s, 1H), 7.61-7.65 (m, 1H), 7.40-7.46 (m, 2H), 6.85-7.08 (m, 4H), 3.65 (s, 3H); MS m/z: 399(M+H$^+$). Calculated for C$_{21}$H$_{18}$N$_8$O: 398.16

Compound (178): $^1$H NMR (DMSO-$d_6$) δ (ppm) 14.26 (s, 1H), 12.96 (s, 1H), 11.24 (s, 1H), 10.17 (s, 1H), 8.35-8.72 (m, 3H), 7.58-8.14 (m, 6H), 5.05-7.22 (m, 2H); MS m/z: 394(M+H$^+$). Calculated for C$_{21}$H$_{15}$N$_9$: 393.15

Compound (179): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.45 (s, 1H), 8.35-8.37 (d, 1H, J=0.057Hz), 8.23-8.26 (m, 1H), 7.88-7.91 (m, 2H), 7.61-7.64 (m, 1H), 7.04-7.08 (m, 1H),

6.87-6.92 (m, 2H), 5.50-6.54 (m, 1H), 3.88(s, 3H), 3.77 (s, 3H); MS m/z: 429 (M+H$^+$). Calculated for $C_{22}H_{20}N_8O_2$: 428.15

Compound (180): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.55 (s, 1H), 8.32-8.38 (m, 1H), 8.23-8.25 (m, 1H), 7.90-7.93 (t, 1H), 7.60-7.63 (m, 1H), 7.34-7.38 (m, 2H), 7.05-7.08 (m, 1H), 6.85-6.90 (m, 3H), 2.87-2.94 (m, 6H); MS m/z: 412 (M+H$^+$). Calculated for $C_{22}H_{21}N_9$: 411.19

Compound (181): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.496 (s, 1H), 8.33-8.35 (m, 1H), 8.22-8.25 (m, 1H), 7.906-7.908 (d, 1H), 7.779-7.808 (d, 1H), 7.607-7.636 (d, 1H), 7.01-7.06 (m, 1H), 6.85-6.89 (m, 1H), 6.55-6.65 (m, 2H), 3.81-3.89 (m, 6H); MS m/z: 429 (M+H$^+$). Calculated for $C_{22}H_{20}N_8O_2$: 428.17

Compound (182): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.28 (s, 1H), 8.16-8.17 (d, 1H), 7.71-7.74 (d, 2H), 7.26-7.32 (t, 2H), 6.96-7.01 (t, 1H), 6.76-6.85 (m, 3H), 6.13 (s, 1H), 3.69-3.78 (m, 6H); MS m/z: 389 (M+H$^+$). Calculated for $C_{21}H_{20}N_6O_2$: 388.16

Compound (183): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.36 (s, 1H), 8.32-8.33 (m, 1H), 7.51 (s, 1H), 7.16-7.25 (m, 4H), 7.03-7.07 (m, 1H),, 6.85-6.90 (m, 1H), 6.52-6.60 (m, 2H), 3.78-3.80 (d, 6H); MS m/z: 389 (M+H$^+$). Calculated for $C_{21}H_{20}N_6O_2$: 388.16

Compound (184): $^1$H NMR (DMSO-$d_6$) δ (ppm) 13.55 (s, 1H), 11.0 (s, 1H), 9.6 (s, 1H), 8.25-8.44 (m, 2H), 7.00-7.91 (m, 11H ); MS m/z: 329(M+H$^+$). Calculated for $C_{19}H_{16}N_6$: 328.14

Compound (185): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.34 (s, 1H), 7.89 (s, 1H), 6.96-7.40 (m, 9H), 6.60 (s, 1H), 3.74-3.80(m, 3H); MS m/z: 359(M+H$^+$). Calculated for $C_{20}H_{18}N_6O$: 358.15

Compound (186): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.13 (s, 1H), 6.65-6.88 (m, 4H), 6.51 (s, 2H), 6.35 (s, 2H), 6.05 (s, 1H), 4.75 (s, 2H), 3.75 (m, 12H); MS m/z: 463(M+H$^+$). Calculated for $C_{24}H_{26}N_6O_4$: 462.20

Compound (187): $^1$H NMR (DMSO-$d_6$) δ (ppm) 13.35 (s, 1H), 9.45(s, 1H), 8.12 (s, 2H), 7.06-7.25 (m, 2H), 6.70-6.74 (m, 1H), 6.37-6.51 (m, 4H), 4.70-4.72 (d, 2H), 3.62-3.72 (m, 9H); MS m/z: 433 (M+H$^+$). Calculated for $C_{23}H_{24}N_6O_3$: 432.19

Compound (188): $^1$H NMR (DMSO-$d_6$) δ (ppm) 13.25 (s, 1H), 9.32 (s, 1H), 8.92-8.99 (d, 1H), 8.08-8.39 (m, 2H), 7.40-7.45 (m, 2H), 6.38 –6.86 (m, 6H), 4.66-4.73 (m, 2H), 3.68-3.71 (m, 9H); MS m/z: 433 (M+H$^+$). Calculated for $C_{23}H_{24}N_6O_3$: 432.19

Compound (189): $^1$H NMR (DMSO-$d_6$) δ (ppm) 12.17 (s, 1H), 8.09-8.66 (m, 4H), 7.85-7.98 (m, 1H), 6.27-6.70 (m, 6H), 4.67-4.70 (m, 2H), 3.65-3.90 (m, 12H); MS m/z: 463 (M+H$^+$). Calculated for $C_{24}H_{26}N_6O_4$: 462.20

Compound (190): $^1$H NMR (DMSO-$d_6$) δ (ppm) 11.76 (s, 1H), 10.02 (s, 1H), 8.74 (s, 1H), 8.14-8.18 (m, 2H), 7.61 (m, 4H), 6.72-6.77 (m, 1H), 6.38-6.52 (m, 3H), 4.70-4.71 (d, 2H), 3.70 (s, 6H); MS m/z: 428 (M+H$^+$). Calculated for $C_{23}H_{21}N_7O_2$: 427.18

Compound (191): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.72 (s, 1H), 8.25-8.28 (m, 2H), 8.09-8.16 (m, 1H), 7.99-8.00 (d, 1H), 7.79-7.80 (t, 1H), 6.87-6.96 (m, 1H), 6.70-6.75 (m, 1H), 6.35-6.52 (m, 4H), 4.69-4.71 (d, 2H), 3.69-3.83 (m, 12H); MS m/z: 463 (M+H$^+$). Calculated for $C_{24}H_{26}N_6O_4$: 462.20

Compound (192): $^1$H NMR (DMSO-$d_6$) δ (ppm) 9.11 (s, 1H), 8.42 (s, 1H), 8.10-8.20 (d, 2H), 7.31-7.434 (d, 2H), 6.38-6.67 (m, 6H), 4.69 (s, 2H), 3.69 (s, 6H), 2.81 (s, 6H); MS m/z: 446 (M+H$^+$). Calculated for $C_{24}H_{27}N_7O_2$: 445.22

Compound (193): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.58 (s, 1H), 8.42-8.45 (m, 1H), 8.10-8.25 (m, 2H), 7.67-7.75 (m, 1H), 7.30-7.40 (m, 2H), 6.70-6.82 (m, 2H), 6.00-6.05 (d, 1H), 4.76-4.84 (d, 2H), 3.70-3.75 (m, 6H) ; MS m/z: 404 (M+H$^+$). Calculated for $C_{21}H_{21}N_7O_2$: 403.18

5

Compound (194): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.45 (s, 1H), 8.26-8.28 (m, 1H), 8.07-8.08 (m, 1H), 7.93-7.95 (m, 1H), 7.72-7.74 (d, 1H), 7.21-7.26 (m, 1H), 6.99-7.08 (m, 2H), 6.83-6.86 (m, 1H), 6.56-6.61 (m, 1H), 6.37-6.40 (m, 1H), 4.69 9s, 2H), 3.65 (s, 3H); MS m/z: 374 (M+H$^+$). Calculated for $C_{20}H_{18}N_7O$: 373.18

10

Compound (195): $^1$H NMR (DMSO-$d_6$) δ (ppm) 9.19 (s, 1H), 8.60-8.61 (d, 1H), 8.43-8.48 (m, 1H), 8.12-8.20 (m, 2H), 7.74-7.77 (m, 1H), 7.33-7.44 (m, 3H), 6.70-6.85 (m, 3H) 4.77-4.79 (d, 2H), 3.71 (s, 3H); MS m/z: 374 (M+H$^+$). Calculated for $C_{20}H_{18}N_7O$: 373.18

15

Compound (196): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.59 (s, 1H), 8.44-8.46 (m, 2H), 8.21 (br, s, 1H), 8.09-8.10 (m, 1H), 7.85-7.88 (m, 1H), 7.73-7.88 9m, 1H), 7.31-7.36 (m, 1H), 6.63-6.73 (m, 2H), 6.44-6.69 (m, 1H), 4.76-4.78 (m, 2H), 3.67-3.84 (m, 6H); MS m/z: 404 (M+H$^+$). Calculated for $C_{21}H_{21}N_7O_2$: 403.18

20

Compound (197): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.10-8.12 (m, 2H), 7.93-7.94 (m, 2H), 7.71-7.74 (m, 1H), 7.30-7.36 (m, 1H), 6.92-6.95 (m, 1H), 6.71-6.76 (m, 1H), 6.43-6.47 (m, 1H), 4,78-4.80 (d, 2H), 3.71-3.83 (m, 6H); MS m/z: 404 (M+H$^+$). Calculated for $C_{21}H_{21}N_7O_2$: 403.18

25

Compound (198): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.06 (s, 1H), 8.77-8.79 (d, 1H), 8.45-8.47 (m, 1H), 8.17-8.26 (m, 2H), 7.66-7.84 (m, 5H), 7.32-7.37 (m, 1H), 6.74-6.79 (m, 1H), 4.79-4.81 (d, 2H); MS m/z: 369 (M+H$^+$). Calculated for $C_{20}H_{16}N_8$: 368.15

Compound (199): $^1$H NMR (DMSO-$d_6$) δ (ppm) 9.02 (s, 1H), 8.60-8.61 (d, 1H), 8.46-8.47 (m, 1H), 8.10-8.19 (m, 2H), 7.74-7.77 (d, 1H), 7.30-7.37 (m, 3H), 6.66-6.74 (m, 3H), 4.77-4.79 (d, 2H), 2.82 (s, 6H); MS m/z: 387 (M+H$^+$). Calculated for $C_{21}H_{22}N_8$: 386.20

5    Compound (200): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.89 (s, 1H), 10.20 (s, 1H), 8.33-8.38 (m, 1H), 8.01-8.04 (m, 1H), 7.22-7.33 (m, 2H), 7.10-7.22 (m, 1H), 7.01-7.09 (m, 3H), 6.62-6.69 (m, 1H), 6.21-6.25 (m, 1H), 3.78-3.87 (m, 9H); MS m/z: 420 (M+H$^+$) Calculated for $C_{22}H_{21}N_5O_4$: 419.43

10   Compound (201): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.40-8.45 (m, 2H), 7.74-7.80 (m, 1H), 7.42-7.45 (d, 2H), 7.08-7.35 (m, 3H), 6.94-6.98 (m, 3H), 6.95-6.98 (m, 1H), 4.59 (s, 2H), 3.75 (s, 3H); MS m/z: 373 (M+H$^+$). Calculated for $C_{21}H_{20}N_6O$: 372.17

Compound (202): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.55-9.35 (m, 3H), 7.80-8.20 (m, 2H), 15   7.20-7.55 (m, 5H), 6.61-6.96 (m, 4H), 4.79 (s, 2H), 3.80 (s, 3H); MS m/z: 373 (M+H$^+$). Calculated for $C_{21}H_{20}N_6O$: 372.17

Compound (203): $^1$H NMR (DMSO-$d_6$) δ (ppm) 11.39 (s, 1H), 8.00-8.57 (m, 3H), 7.68-7.98 (m, 6H), 7.36-7.41 (m, 3H), 6.74-6.83 (m, 2H), 4.70-4.72 (d, 2H); MS m/z: 369 20   (M+H$^+$). Calculated for $C_{21}H_{17}N_7$: 367.15

Compound (204): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.69 (s, 1H), 7.75 (s, 1H ), 7.60-7.62 (d, 1H), 7.23-7.32 (m, 5H), 7.11-7.13 (d, 1H), 6.92-6.95 (d, 2H), 6.82-6.85 (d, 1H), 6.71-6.76 (t, 1H), 6.58-6.61 (d, 1H), 4.46-4.48 (d, 2H), 3.74-3.76 (d, 6H); MS m/z: 403 (M+H$^+$). 25   Calculated for $C_{23}H_{22}N_4O_3$: 402.17

Compound (205): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.71 (s, 1H), 7.82-7.88 (t, 1H), 7.60-7.65 (m, 1H), 7.10-7.46 (m, 8H), 6.70-6.85 (m, 2H), 6.55-6.62 (m, 1H), 5.54-4.58 (m, 2H), 3.78 (s, 3H); MS m/z: 391 (M+H$^+$). Calculated for $C_{22}H_{19}FN_4O_2$: 390.15

30

Compound (206): $^1$H NMR (DMSO-$d_6$) δ (ppm) 7.91-7.94 (t, 1H), 7.60-7.62 (d, 1H), 7.10-7.41 (m, 8H), 6,67-6.77 (m, 2H), 6.55-6.58 (m, 1H), 4.57-4.59 (m, 1H), 4,57-4.59 (d, 2H), 3.76 (s, 3H); MS m/z: 407 (M+H$^+$). Calculated for $C_{22}H_{19}ClN_4O_2$: 406.12

Compound (207): $^1$H NMR (DMSO-$d_6$) δ (ppm) 8.24-8.26 (m, 1H), 8.08-8.12 (t, 1H), 7.86-7.89 (m, 1H), 6.77-7.00 (m, 6H), 6.19-6.20 (t, 1H), 6.00 (s, 2H), 3.74 (s, 6H); MS m/z: 404 (M+H$^+$). Calculated for $C_{22}H_{21}N_5O_3$: 403.16

Compound (208): MS m/z: 380 (M+H$^+$)

Compound (209): $^1$H NMR (CDCl$_3$) δ (ppm) 8.32-8.40 (m, 2H), 7.10-7.26 (m, 2H), 6,70-6.89 (m, 3H), 4.09-4.12 (m, 2H), 3.83 (s, 3H), 3.10-3.17 (m, 4H), 2.54-2.60 (m, 4H), 2.27 (s, 3H); MS m/z: 365 (M+H$^+$)

Compound (210): MS m/z: 395 (M+H$^+$)

Compound (211): $^1$H NMR (DMSO-$d_6$) δ (ppm) 10.63 (s, 1H), 7.54-7.55 (d, 1H), 7.12-7.52 (m, 4H), 6.87-6.90 (d, 1H), 6.59-6.70 (m, 4H), 3.77 (s, 3H); MS m/z: 283 (M+H$^+$). Calculated for $C_{15}H_{14}N_{4O2}$: 282.11

Compound (212): $^1$H NMR (methanol-$d_4$) δ (ppm) 7.83-7.84 (d, 1H), 7.70-7.73 (d, 1H), 7.12-7.18 (m, 1H), 6.81-6.88 (m, 2H), 6.70-6.73 (m, 1H), 6.41-6.45 (m, 1H), 3.77-3.87 (d, 6H); MS m/z: 312 (M+H$^+$). Calculated for $C_{16}H_{17}N_5O_2$: 311.14

Compound (213): $^1$H NMR (methanol-$d_4$) δ (ppm) 7.71-7.74 (d, 1H), 7.30-7.33 (d, 2H), 7.09-7.15 (m, 1H), 6.79-6.84 (m, 3H), 6.66-6.71 (m, 1H), 2.83-2.85 (d, 6H); MS m/z: 295 (M+H$^+$). Calculated for $C_{16}H_{18}N_6$: 294.16

Compound (214): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.28-8.29 (m, 1H), 8.10-8.12 (m, 1H), 7.84-7.97 (m, 2H), 7.95-7.05 (m, 3H), 3.74-3.79 (m, 4H), 2.52-2.54 (m, 4H), 2.24 (s, 3H); MS m/z: 351(M+H$^+$)

5     Compound (215): $^1$H NMR (methanol-$d_4$) δ (ppm) 8.15-8.22 (m, 3H), 7.82-7.90 (m, 1H), 7.50-7.63 (m, 3H), 6.90-6.94 (m, 1H), 3.25-3.45 (m, 4H), 2.43-2.48 (m, 4H), 2.15-2.20 (m, 3H); MS m/z: 389(M+H$^+$)

Compound (216): $^1$H NMR (CDCl$_3$) δ (ppm) 8.33-8.36 (m, 1H), 8.06-8.09 (m, 1H), 7.71-

10    7.74 (m, 1H), 7.63 (s, 1H), 6.83-6.89 (m, 2H), 6.03 (s, 2H), 3.28-3.32 (m, 4H), 2.46-2.50 (m, 4H), 2.34 (s, 3H); MS m/z: 365 (M+H$^+$)

2-[5-(3-trifluoromethylphenyl)-1$H$-imidazol-2-yl]aniline (217): *See* Example 13.

15   2-(5-(3-Trifluoromethoxyphenyl)-1H-[1,2,4]-triazol-3-yl)aniline (218): MS m/z:  321 (M+H$^+$) 2.65g (49%). This material was recrystallised from methanol/water.

2-(5-(2-Chlorophenyl)-1H-[1,2,4]-triazol-3-yl)aniline (219): MS m/z: 272 (M+H$^+$) 0.965g (21%).  This material was recrystallised from ethanol/water.

20

2-(5-(3-Methoxyphenyl)-1H-[1,2,4]-triazol-3-yl)aniline (220): MS m/z: 267 (M+H$^+$) 1.2g (28%). This material was recrystallised from methanol.

2-(5-(4-bromophenyl)-1H-[1,2,4]-triazol-3-yl)aniline (221): MS m/z: 316 (M+H$^+$)

25   1.08g (24%). This material was recrystallised from methanol.

2-(5-(3-bromophenyl)-1H-[1,2,4]-triazol-3-yl)aniline (222): MS m/z: 316 (M+H$^+$) – 1.97g (37%). This material was recrystallised from methanol.

<u>2-(5-(4-Trifluoromethoxyphenyl)-1H-[1,2,4]-triazol-3-yl)aniline</u> (**224**): MS m/z: 321 (M+H$^+$); 1.15g (25%). This material was recrystallised from ethanol/water.

<u>2-(5-(4-Trifluoromethylphenyl)-1H-[1,2,4]-triazol-3-yl)aniline</u> (**225**): MS m/z: 305 (M+H$^+$); 1.1g (37%). This material was recrystallised from methanol.

<u>2-(5-(3-Trifluoromethylphenyl)-1H-[1,2,4]-triazol-3-yl)aniline</u> (**226**): MS m/z: 305 (M+H$^+$); 1.1g (30%). This material was recrystallised from methanol.

Example 19

<u>Homogeneous Time-Resolved Fluorescence (HTRF) Assay</u>
<u>for VEGFR-2 (KDR) Kinase Inhibition</u>

Representative compounds of the invention were tested for their inhibition of VEGFR (KDR) tyrosine kinase. The percent inhibition and IC$_{50}$ values of selected compounds were determined. These results are summarized in Table 5.

Table 5

| KDR Enzymatic Assay | | |
| --- | --- | --- |
| Cmpd. No. | % Inhibition | IC$_{50}$ (μM) |
| 1 | 91 | |
| 2 | 67 | |
| 3 | 85 | |
| 4 | 69 | |
| 5 | 27 | |
| 6 | 41 | |
| 7 | 18 | |
| 8 | 34 | |
| 9 | 60 | |
| 11 | 71 | |
| 12 | 55 | |
| 13 | 34 | |
| 14 | 26 | |

| Cmpd. No. | % Inhibition | IC$_{50}$ (μM) |
|-----------|--------------|----------------|
| 15 | 83 | |
| 16 | 90 | |
| 17 | 19 | |
| 18 | 70 | |
| 19 | 77 | 4 |
| 20 | 52 | |
| 21 | 8 | |
| 22 | 61 | 3.6 |
| 23 | 75 | 2.3 |
| 24 | 70 | 1.3 |
| 25 | 74 | 1.8 |
| 26 | 86 | |
| 27 | 72 | 0.52 |
| 28 | 69 | 2.3 |
| 34 | 66 | |
| 42 | 66 | |
| 50 | 31 | |
| 51 | 48 | 15 |
| 52 | 53 | 11 |
| 53 | 52 | 11 |
| 54 | 20 | |
| 55 | 64 | 4.5 |
| 56 | 50 | |
| 58 | 40 | |
| 60 | 69 | 4.1 |
| 61 | | 4.1 |
| 62 | 79 | 1.8 |
| 64 | 10 | |
| 76 | 62 | |
| 77 | 40 | |
| 78 | 7 | |
| 79 | 17 | |
| 87 | 18 | |
| 88 | 39 | |
| 89 | 67 | |
| 90 | 78 | |
| 91 | 71 | |
| 93 | 26 | |
| 102 | 65 | |

| Cmpd. No. | % Inhibition | IC$_{50}$ (µM) |
|---|---|---|
| 117 | 10 | |
| 118 | 81 | |
| 119 | 11 | |
| 120 | 3 | |
| 121 | 6 | |
| 125 | 12 | |
| 126 | 12 | |
| 127 | 6 | |
| 128 | 4 | |
| 129 | 8 | |
| 130 | 4 | |
| 132 | 8 | |
| 133 | 5 | |
| 134 | 5 | |
| 135 | 5 | |
| 136 | 3 | |
| 137 | | 24 |
| 138 | 43 | |
| 139 | 7 | |
| 140 | 4 | |
| 141 | 9 | |
| 142 | 3 | |
| 143 | | 24 |
| 144 | 25 | |
| 145 | 3 | |
| 146 | 85 | |
| 147 | | 0.27 |
| 148 | 30 | |
| 149 | 33 | |
| 150 | 245 | |
| 151 | 90 | |
| 152 | 8 | |
| 155 | 19 | |
| 156 | 39 | |
| 157 | 18 | |
| 159 | 25 | |
| 160 | 28 | |
| 161 | 42 | |
| 162 | 11 | |
| 163 | 14 | |

| Cmpd. No. | % Inhibition | IC$_{50}$ (μM) |
|-----------|--------------|----------------|
| 164 | 51 | |
| 165 | 51 | |
| 166 | 72 | |
| 167 | 47.5 | |
| 168 | 46 | |
| 169 | 55 | |
| 170 | 63 | |
| 171 | 55 | |
| 172 | 61 | |
| 173 | 58 | |
| 174 | 59 | |
| 175 | 72 | |
| 176 | 82 | |
| 178 | 35 | |
| 179 | 70 | |
| 180 | 84 | |
| 181 | 84 | |
| 182 | 9 | |
| 183 | 29 | |
| 185 | 73 | |
| 186 | 18 | |
| 187 | 12 | |
| 188 | 18 | |
| 189 | 41 | |
| 190 | 14 | |
| 191 | 41 | |
| 192 | 23 | |
| 193 | 79 | |
| 194 | 81 | |
| 195 | 85 | |
| 196 | 81 | |
| 200 | -2 | |
| 201 | 74 | |
| 202 | 81 | |
| 203 | 42 | |
| 204 | 14 | |
| 208 | 2 | |
| 212 | 54 | |
| 216 | 20 | |

VEGFR tyrosine kinase inhibition is determined by measuring the phosphorylation

level of poly-Glu-Ala-Tyr-biotin (pGAT-biotin) peptide in a Homogeneous Time-

Resolved Fluorescence (HTRF) assay. Into a black 96-well Costar plate is added 2 µl/well

of 25x compound in 100% DMSO (final compound concentration in the 50-µl kinase

5      reaction is typically 1 nM to 10 µM). Next, 38 µl of reaction buffer (25 mM Hepes

pH 7.5, 5 mM MgCl2, 5 mM MnCl2, 2 mM DTT, 1 mg/ml BSA) containing 0.5 pmoles

polyGAT-biotin and 3-4 ng KDR enzyme is added to each well. After 5-10 min

preincubation, the kinase reaction is initiated by the addition of 10 µl of 10 µM ATP in

reaction buffer, after which the plate is incubated at room temperature for 45 min. The

10     reaction is stopped by the addition of 50 µl of KF buffer (50 mM Hepes pH 7.5, 0.5 M KF,

1 mg/ml BSA) containing 100 mM EDTA and 0.36 µg/ml PY20K (Eu-cryptate labeled

anti-phosphotyrosine antibody, CIS bio international). After 30 min, 100 µl of 5 nM SV-

XL (modified-APC-labeled Streptavidin, CIS bio international) in KF buffer is added, and

after an addition 2-hr incubation at room temperature, the plate is read in a RUBYstar

15     HTRF Reader.


Example 20

Cell-based assay for VEGFR-2 (KDR) Kinase Inhibition

Representative compounds of the invention were tested using the ELISA

20     Cell-based assay for KDR inhibition. The results are reported in Table 6.


Table 6

| Cell-Based Phosphorylation | | |
|---|---|---|
| Cmpd. No. | % Inhibition | IC$_{50}$ (µM) |
| 1 | 78 | 14 |
| 2 | 34 | |
| 3 | 38 | |
| 4 | 50 | 30 |
| 5 | 10 | |
| 6 | 30 | |
| 7 | 58 | 30 |
| 9 | 47 | |

| Cmpd. No. | % Inhibition | IC$_{50}$ (µM) |
|---|---|---|
| 10 | 36 | |
| 11 | 0 | |
| 12 | 70 | 5 |
| 13 | 63 | 30 |
| 14 | 15 | |
| 15 | 75 | 10 |
| 16 | 91 | 10 |
| 17 | 76 | 30 |
| 18 | 77 | 1 |
| 76 | 53 | 10 |
| 77 | 15 | |
| 78 | 0 | |
| 156 | 70 | |
| 157 | 57 | |
| 159 | 67 | |
| 161 | 68 | |
| 164 | 69 | 20 |
| 165 | 60 | |
| 166 | 68 | |
| 167 | 62 | |
| 168 | 71 | |
| 169 | 63 | |
| 170 | 67 | |
| 171 | 67 | |
| 172 | 70 | 4.7 |
| 173 | 68 | |
| 174 | 68 | 5.6 |
| 175 | 64 | |
| 176 | 66 | 2.6 |
| 179 | 68 | |
| 180 | 59 | |
| 181 | 66 | 1.1 |
| 201 | 64 | |
| 202 | 60 | |
| 203 | 19 | |
| 205 | | 9 |
| 207 | | 193 |
| 212 | 65 | |

Transfection of 293 cells with DNA expressing FGFR1/KDR chimera: DNA for
transfection was diluted to a final concentration of 5 μg/ml DNA in 1XBBS, 125 mM
CaCl₂ and incubated at room temperature for 30 min. 293 cells were seeded in 15 cm
tissue culture plates using 2 x10⁷ cells per plate and incubated for 4 hrs, followed by
5      dropwise addition of 3 ml of DNA solution. The plates were incubated overnight.

The next morning, the cells were trypsinized, collected by centrifugation,
resuspended (4 x 10⁵ cell/ml), divided into wells of 48 well tissue culture plates (1
ml/well) and incubated overnight. Compounds of the invention were added to individual
wells to a final concentration of 10-30 μM and incubated for 2 hours. Generally, 10 mM
10     stock solution were diluted 1/300-1/1000, yielding a final DMSO concentration of
0.1-0.3%. Cells were lysed by resuspension in Lysis buffer (150 mM NaCl, 50 mM Hepes
pH 7.5, 0.5% Trition X-100, 10 mM NaPPi, 50 mM NaF, 1 mM Na₃VO₄) and rocked for
1h at 4°C. Cells were lysed by adding in 100 μl lysis buffer per well.


15     ELISA for Detection of Tyrosine-phosphorylated Chimeric Receptor: 96 well ELISA
plates were coated using 100 μl/well of 10 μg/ml αFGFR1, and incubated overnight at 4°C.
αFGFR1 is prepared in a buffer made with 16 ml 0.2M Na₂CO₃ and 34 ml 0.2M NaHCO₃
and the pH adjusted to 9.6. Concurrent with lysis of the transfected cells, αFGFR1 coated
ELISA plates are washed three times with PBS+0.1% Tween-20, blocked by addition of
20     200 μl/well of 3% BSA in PBS and incubated for 1h. Blocking solution is removed from
the wells. 80 μl of lysate is then transferred to the coated and blocked wells and incubated
for 1h at 4°C. The plates are washed three times with PBS+0.1% Tween-20.
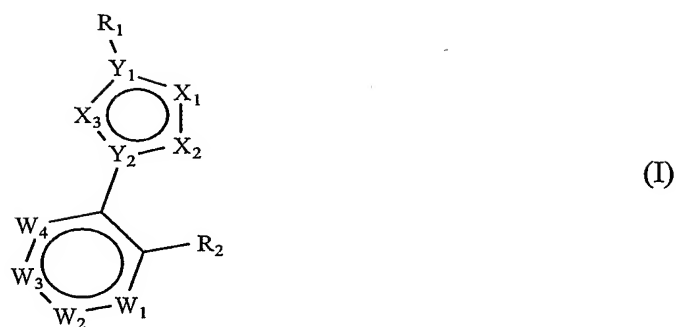
To detect bound phosphorylated chimeric receptor, 100 μl of anti-phosphotyrosine
antibodies (RC20:HRPO, Transduction Laboratories) were added per well (final
25     concentration 0.5 μg/ml in PBS) and incubated for 1h. The plates were washed six times
with PBS+0.1% Tween-20. Enzymatic activity of HRP was detected by adding 50 μl/well
of equal amounts of the Kirkegaard & Perry Laboratories (KPL) Substrate A and Substrate
B. (KPL cat. #54-61-0). The reaction was stopped by the addition of 50 μl/well 0.1N
H₂SO₄ and absorbance is detected at 450nm

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The above examples are intended to be illustrative only. In particular, the invention is not intended to be limited to the methods, protocols, conditions and the like specifically recited herein, insofar as those skilled in the art would be able to substitute other conditions, methods, amounts, materials, etc. based on the present disclosure to

5 arrive at compounds within the scope of this disclosure. While the present invention is described with respect to particular examples and preferred embodiments, the present invention is not limited to these examples and embodiments. In particular, the compounds of the present invention are not limited to the exemplary species' recited herein. Moreover, the methods of the present invention are not limited to treating only the exemplified

10 diseases and conditions, but rather any disease or condition that may be treated by regulation of kinases. Additionally, the methods of synthesis of the present invention are not limited to the methods exemplified in the example. The methods of the present invention include methods of making any of the compounds set forth in the present invention that those skilled would be able to make in view of the present disclosure, and

15 are not limited to the exemplified method. For example, methods encompassed by the present invention may involve the use of a different starting material depending on the desired final compound, different amounts of various ingredients, or substitution of different ingredients such as other reactants or catalysts that would be suitable depending on the starting material and result to be achieved.

CLAIMS

What is claimed is:

1.      A compound of Formula (I):



(I)

wherein :

$X_1$ and $X_2$ are atoms or radicals independently selected from the group consisting of oxygen, sulfur, nitrogen, radicals of formula $C-R_3$ and radicals of formula $N-R_3$, with the proviso that at least one of $X_1$ and $X_2$ is oxygen, sulfur, nitrogen or a diradical of formula $N-R_3$, wherein:

R_3 is an atom or radical selected from the group consisting of:

1)      hydrogen,

2)      halogen,

3)      alkyl, optionally substituted with one or more substituents selected from R_4;

4)      alkenyl, optionally substituted with one or more substituents selected from R_4;

5)      alkynyl, optionally substituted with one or more substituents selected from R_4;

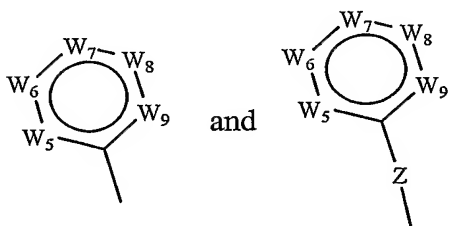wherein R_4 is an atom or radical selected from the group consisting of:

a)      halogen;

b)      alkyl, which may be optionally substituted with one or more

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halogen, hydroxy or lower alkoxy;

c)    alkenyl, which may be optionally substituted with one or more halogen, hydroxy or lower alkoxy;

d)    nitro;

e)    cyano;

f)    oxo;

g)    vinyl;

h)    styryl;

i)    a group of formula $-C(O)R_5$, $-CO_2R_5$, $-OR_5$, $-SR_5$, $-SOR_5$, $-SO_2R_5$, $-NR_5R_6$, $-NCO_2R_5$, or $-OCO_2R_5$ where $R_5$ and $R_6$ are atoms or radicals independently selected from the group consisting of hydrogen, lower alkyl, aralkyl, aryl and heteroaryl;

$X_3$ is selected from the group consisting of oxygen, sulfur, nitrogen and diradicals of formula $N-R_3$,

$Y_1$ and $Y_2$ are atoms independently selected from the group consisting of nitrogen and carbon,
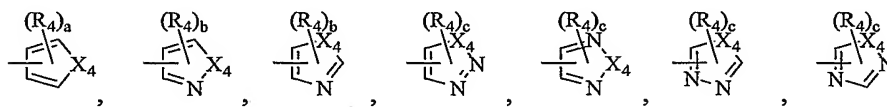
$R_1$ is a radical selected from the group consisting of:



wherein $W_1$ is nitrogen or $C-R_{w1}$, $W_2$ is nitrogen or $C-R_{w2}$, $W_3$ is nitrogen or $C-R_{w3}$, $W_4$ is nitrogen or $C-R_{w4}$, $W_5$ is nitrogen or $C-R_{w5}$, $W_6$ is nitrogen or $C-R_{w6}$, $W_7$ is nitrogen or $C-R_{w7}$, $W_1$ is nitrogen or $C-R_{w8}$ and $W_9$ is nitrogen or $C-R_{w9}$, each $R_{w1}$, $R_{w2}$, $R_{w3}$, $R_{w4}$, $R_{w5}$, $R_{w6}$, $R_{w7}$, $R_{w8}$ and $R_{w9}$ being an atom or radical independently selected from the group consisting of:

1)    hydrogen,

2)    halogen,

3)    nitro,

4)      cyano,

5)      alkyl, optionally substituted with one or more substituents selected
        from $R_4$,

6)      alkenyl, optionally substituted with one or more substituents
        selected from $R_4$,

7)      alkynyl, optionally substituted with one or more substituents
        selected from $R_4$,

8)      aralkyl, optionally substituted with one or more substituents selected
        from $R_4$,

9)      phenyl, optionally substituted with 1 to 5 substituents selected from
        $R_4$,

10)     a group of the formula $-CO_2R_5$, $-COR_5$, $-OR_5$, $-SR_5$, $-SOR_5$, $-SO_2R_6$,
        $-NR_5R_6$,

11)     pyridyl, optionally substituted with 1 to 4 substituents selected from
        $R_4$,

12)     pyrazinyl, optionally substituted with 1 to 3 substituents selected
        from $R_4$,

13)     pyrimidinyl, optionally substituted with 1 to 3 substituents selected
        from $R_4$,

14)     indazolyl, optionally substituted with 1 to 5 substituents selected
        from $R_4$,

15)     tetrazolyl, and

14)     heterocyclic radicals of formulae:



wherein $X_4$ is O, S, or $N-R_4$,

        *a* is 0 to 3,

        *b* is 0 to 2,

        *c* is 0 or 1, or

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together, one or more of the combinations $R_{w1}$ and $R_{w2}$, $R_{w2}$ and $R_{w3}$, $R_{w3}$ and $R_{w4}$, $R_{w5}$ and $R_{w6}$, $R_{w6}$ and $R_{w7}$, $R_{w7}$ and $R_{w8}$, and $R_{w8}$ and $R_{w9}$ form a fused 5- or 6- membered carbocyclic ring or heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen and sulfur,

Z is selected from the group consisting of oxygen, sulfur, $-S(O)-$, $-S(O)_2-$, $-CR_5R_6-$, $-CR_5R_6O-$, $CR_5R_6NR_3-$ and $-NR_3-$

$R_2$ is a radical of formula $-OR_{7a}$, $-SR_{7a}$, $-S(O)R_{7a}$, $-CR_5R_6R_{7a}$, $-CR_5R_6-OR_{7a}$

wherein $R_{7a}$ is a radical selected from the group consisting of:

1)      $-CH_2-R_8$,

2)      $-CH_2CH_2-R_8$,

3)      $-CH_2CH_2CH_2-R_8$, and

4)      $-R_8$,

         wherein $R_8$ is a cyclic radical selected from the group consisting of:

         a)      aromatic carbocyclic radicals, optionally substituted with 1 to 5 substituents wherein the substituents are selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$, and

         b)      aromatic and non-aromatic heterocyclicyl radicals, optionally substituted with 1 to 5 substituents wherein the substituents are either selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$, or

$R_2$ is a radical selected from the group consisting of $-CR_5R_6NR_{7a}R_{7b}$, and $-NR_{7a}R_{7b}$ and:

     $R_{7a}$ and $R_{7b}$ are both hydrogen,

     $R_{7a}$ and $R_{7b}$ together form a 6 membered ring heterocycle, optionally substituted with one or more substituents selected from the group $R_4$, or

$R_{7b}$ is hydrogen or a radical selected from $R_4$ and $R_{7a}$ is a radical selected from the group consisting of:

1)     $-CH_2-R_8$,

2)     $-CH_2CH_2-R_8$,

3)     $-CH_2CH_2CH_2-R_8$, and

4)     $-R_8$,

wherein $R_8$ is a cyclic radical selected from the group consisting of:

a)     aromatic carbocyclic radicals, optionally substituted with 1 to 5 substituents wherein the substituents are selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$, and

b)     aromatic and non-aromatic heterocyclicyl radicals, optionally substituted with 1 to 5 substituents wherein the substituents are either selected from $R_4$ or two adjacent substituents can form a 5, 6 or 7 membered fused carbocyclic or heterocyclic ring optionally substituted with one or more substituents selected from $R_4$.

2.     The compound of claim 1 wherein $R_2$ is a radical of formula $-NH-R_8$, $-NHCH_2-R_8$, $-NHCH_2CH_2-R_8$ or $-NHCH_2CH_2CH_2-R_8$, wherein $R_8$ is selected from the group consisting of optionally substituted phenyl radicals, optionally substituted bicyclic aromatic carbocyclic radicals, optionally substituted polycyclic aromatic carbocyclic radicals, optionally substituted monocyclic aromatic heterocyclic radicals, optionally substituted bicyclic aromatic heterocyclic radicals and optionally substituted polycyclic aromatic heterocyclic radicals.

3.     The compound of claim 2 wherein $R_8$ is selected from the group consisting of phenyl, optionally substituted with 1 to 5 substituents selected from $R_4$; pyridinyl,

optionally substituted with 1 to 4 substituents selected from $R_4$; pyrazinyl,

optionally substituted with 1 to 3 substituents selected from $R_4$; pyrimidinyl,

optionally substituted with 1 to 3 substituents selected from $R_4$; indazolyl,

optionally substituted with 1 to 5 subsitutents selected from $R_4$; tetrazolyl; and

aromatic heterocyclic radicals of formula:
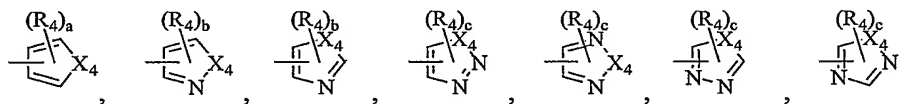


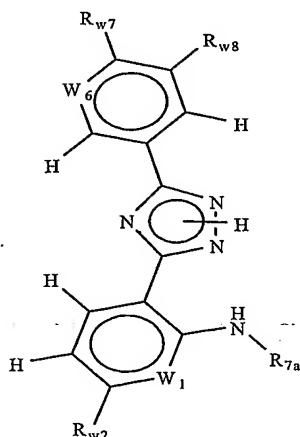wherein X, $R_4$ and a-c are as previously defined.

4.      The compound of claim **1** having the Formula (Ia):
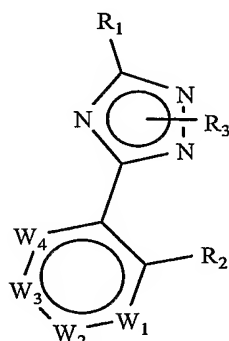


(Ia)

wherein $W_1$, $W_2$, $W_3$, $W_4$, $R_1$, $R_2$ and $R_3$ are as previously defined.
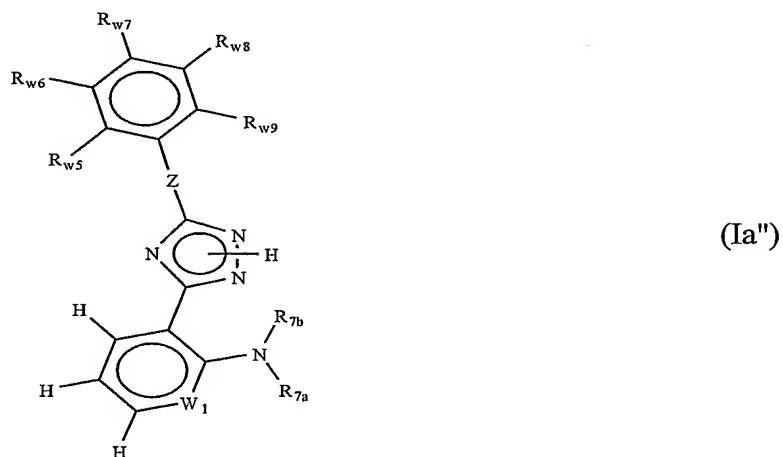
5.      The compound of claim **4** having the Formula (Ia'):



(Ia')

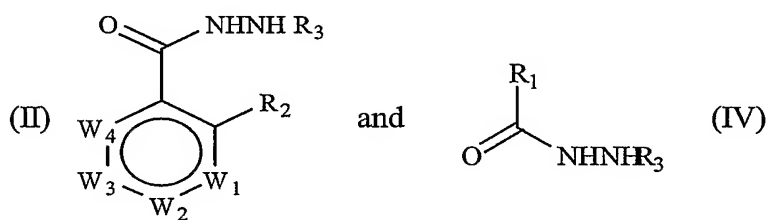wherein $W_1$, $W_6$, $R_{w2}$, $R_{w7}$, $R_{w8}$, and $R_{7a}$ are as previously defined.

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6.      The compound of claim **4** having the Formula (Ia"):



(Ia")

$W_1$, $R_{w5}$, $R_{w6}$, $R_{w7}$, $R_{w8}$, $R_{w9}$, $R_{7a}$, $R_{7b}$ and Z are as previously defined.
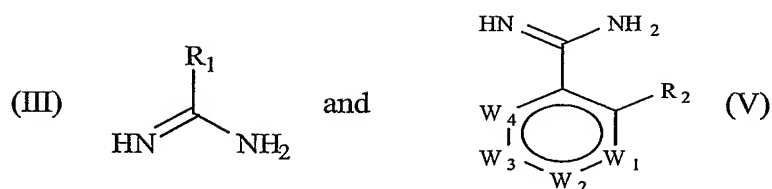
7.      A process comprising:

a)      providing a hydrazide having a formula selected from the group consisting of
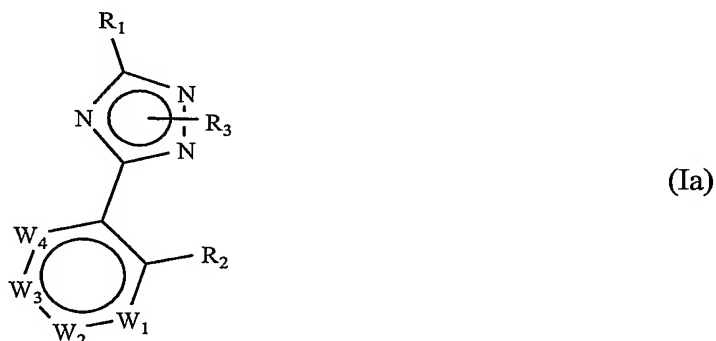


or salt thereof,

b)      providing a complementary amidine having a formula selected from the group consisting of

(III)    and    (V)

or salt thereof,

wherein $R_1$, $R_2$, $R_3$, $W_1$, $W_2$, $W_3$ and $W_4$ are as defined in claim **1**,

c)    contacting the hydrazide and the amidine for a period of time sufficient to substantially convert at least one of the hydrazide and amidine to a compound of Formula (Ia):



(Ia)

and

d)    isolating the compound.

8.    The process of claim **7** wherein the hydrazide is of Formula (II) and the amidine is of Formula (III) .

9.    The process of claim **7** wherein the hydrazide is of Formula (IV) and the amidine is of Formula (V).

10.    The process of claim **7** wherein providing the amidine comprises:

a)    contacting a nitrile with a lower alcohol under acidic conditions to form an imidate or salt thereof, and

b)    contacting the imidate or salt thereof with ammonia to form the amidine.

11. The process of claim **7** wherein providing the hydrazide comprises:

a) contacting a carboxylic acid ester selected from the group consisting of unsubstituted or aryl substituted orthoamino benzene carboxylic acid esters and unsubstituted or aryl substituted (2-amino)-3-pyridinyl carboxylic acid esters, with an aldehyde to form an imine,

b) reducing the imine to a second carboxylic acid ester selected from the group consisting of optionally aryl substituted, N substituted 2-amino benzene carboxylic acid esters and N substituted 3-pyridinyl carboxylic acid esters.

c) and converting the second carboxylic acid ester to the hydrazide with hydrazine.

12. The compound of claim **1** having the Formula (Ib):

(Ib)
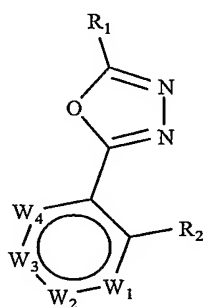
wherein $R_1$, $R_2$, $W_1$, $W_2$, $W_3$ and $W_4$ are as previously defined.

13. The compound of claim **12** having the Formula (Ib'):

(Ib')
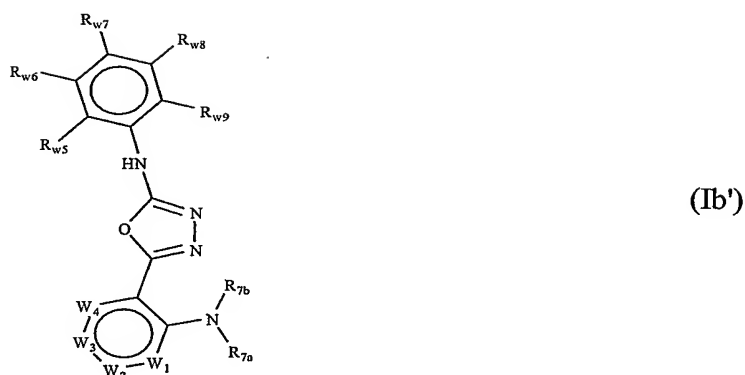
wherein $W_1$, $W_2$, $W_3$, $W_4$, $R_{w5}$, $R_{w6}$, $R_{w7}$, $R_{w8}$, $R_{w9}$, $R_{7a}$ and $R_{7b}$ are as previously defined.

14.    A process comprising:

a)    providing a hydrazide of Formula (II):



(II)

wherein $R_2$ is a radical of formula $-NR_{7a}R_{7b}$,

b)    providing an isothiocyanate of Formula (VI):



(VI)

c)    contacting the hydrazide and isothiocyanate for a period of time sufficient to substantially convert at least one of the hydrazide and isothiocyanate to an intermediate compound, and

d)    contacting the intermediate compound with a coupling agent to convert it into a 1,3,4-oxadiazole of Formula (Ib'):

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(Ib')
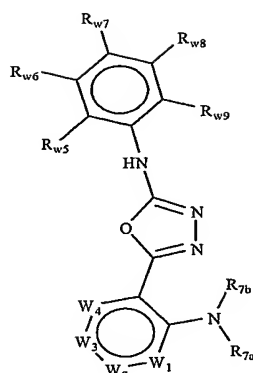
wherein $W_1$, $W_2$, $W_3$, $W_4$, $R_{w5}$, $R_{w6}$, $R_{w7}$, $R_{w8}$, $R_{w9}$, $R_{7a}$, and $R_{7b}$ are as previously defined in claim **13**.

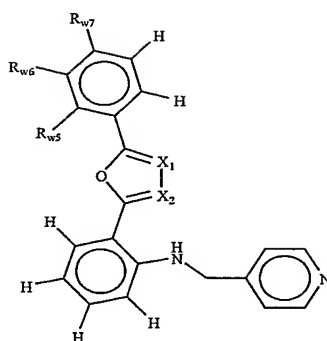15.      The compound of claim **1** having the Formula (Ic):
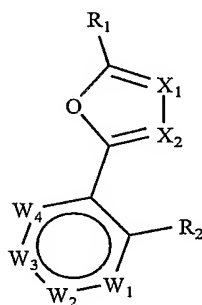


(Ic)

wherein:

1)      $X_1$ is nitrogen and $X_2$ is C-$R_3$, or

2)      $X_1$ is C-$R_3$ and $X_2$ is nitrogen, and

$R_1$, $R_2$, $W_1$, $W_2$, $W_3$ and $W_4$ are as previously defined.
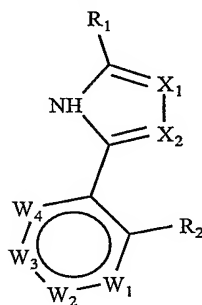
16.      The compound of claim **1** having the Formula (Ic'):

(Ic')

$R_{w5}$, $R_{w6}$ and $R_{w7}$ are as previously defined.

17.     The compound of claim **1** having the Formula (Id):



(Id)

wherein:

1)      $X_1$ is nitrogen and $X_2$ is -$CR_3$, or

2)      $X_1$ is -$CR_3$ and $X_2$ is nitrogen, and

$R_1$, $R_2$, $R_3$, $W_1$, $W_2$, $W_3$ and $W_4$ are as previously defined.

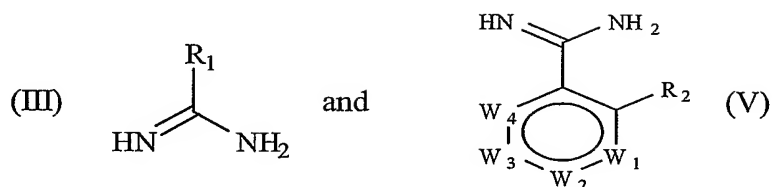18.     A process comprising:

a)      providing an α-halo carbonyl compound having a formula selected from the group consisting of:
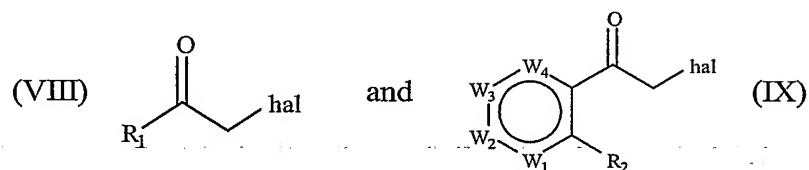


b)      providing a complementary amidine having a formula selected from the

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group consisting of:



(III)                        and                          (V)

c)     contacting the α-halo carbonyl compound and the amidine for a period of
time sufficient to substantially convert at least one of the hydrazide and
amidine to a compound of Formula (Id):



(Id)

and

d)     isolating the compound,

wherein $R_1$, $R_2$, $X_1$, $X_2$ $W_1$, $W_2$, $W_3$ and $W_4$ are as defined in claim **17** and hal is
bromine or iodine.

19.     The compound of claim **17** having the Formula (Id'):



(Id')

wherein $R_3$, $R_{w5}$, $R_{w6}$ and $R_{w7}$ are as previously defined.

20.   A process comprising:

   a)   providing an α-halo carbonyl compound of Formula (III'):



(III')

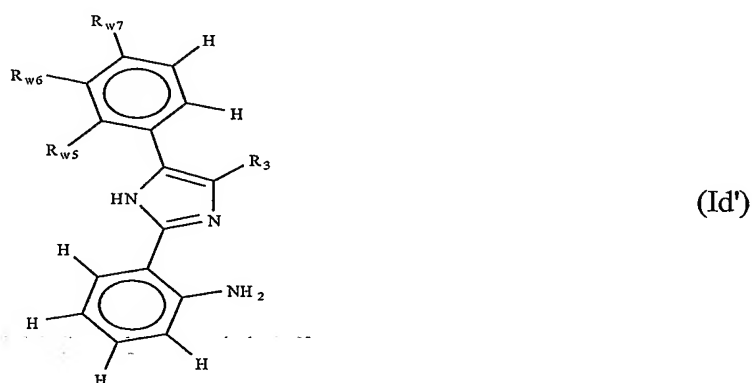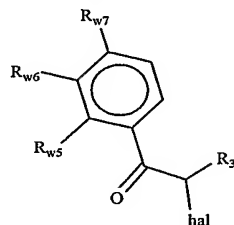   b)   providing an amidine of Formula (IX'):
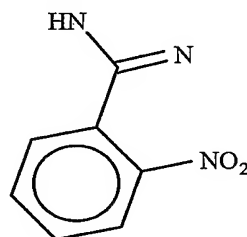


(IX')

   c)   contacting the α-halo carbonyl compound and the amidine for a period of
        time sufficient to substantially convert at least one of the hydrazide and
        amidine to a 2-(2-nitrophenyl)-4-aryl imidazole, and

   d)   reducing the 2-(2-nitrophenyl)-4-aryl imidazole compound to a compound
        of Formula (Id'):



(Id')
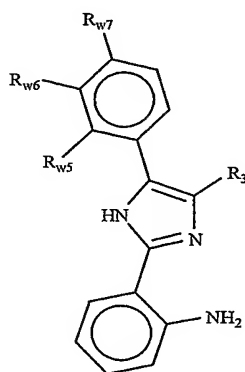
   wherein $R_3$, $R_{w5}$, $R_{w6}$ and $R_{w7}$ are as defined in claim **19** and hal is bromine or
   iodine.

21.     The compound of claim **1** in a condensed state.

22.     The compound of claim **21** wherein the condensed state is a solid.

23.     The compound of claim **22** wherein the solid is amorphous.

24.     The compound of claim **22** wherein the solid is crystalline.

25.     The compound of claim **24** wherein the crystalline solid state is a solvate of the compound and a solvent.

26.     The compound of claim **25** wherein the solvent is water.

27.     The compound of claim **21** wherein the condensed state is a salt of the compound.

28.     The compound of claim **1** that is a solute in a liquid.

29.     The compound of claim **28** wherein the liquid is a body fluid of a mammal selected from the group consisting of blood, bile and gastric fluid.

30.     The compound of claim **1** in at least 98% purity by weight.

31.     A mixture of two or more compounds of claim **30**.

32.     A pharmaceutical composition made by a process comprising contacting a pharmaceutical carrier and a compound of claim **30**.

33.     A pharmaceutical composition comprising a compound of claim **1** and a pharmaceutical carrier.

34.     A pharmaceutical dosage form comprising the pharmaceutical composition of
        claim **33**.

35.     The pharmaceutical dosage form of claim **34** that is selected from the group
        consisting of tablets, capsules, troches, lozenges and soft gelatin capsules.

36.     A method of influencing the progression of an angiogenic dependent disease in a
        mammal comprising administering to the mammal an effective anti-angiogenic
        amount of a compound of Formula (I) as defined in claim **1**.

37.     The method of claim **36** wherein the influence is mediated by restriction of the
        blood supply to diseased cells.

38.     The method of claim **37** wherein the influence on the progression of the angiogenic
        dependent disease is arrest of neovascularization leading to the eradication of the
        disease from the mammal.

39.     The method of claim **37** wherein the influence on the progression of the angiogenic
        dependent disease is partial restriction of the blood supply to diseased cells,
        resulting in an increase in life expectancy of the mammal.

40.     The method of claim **36** wherein the angiogenic dependent disease is selected from
        the group consisting of  malignant tumors, malignant neoplasms, highly vascular
        tumors and neoplasms, brain cancer, genitourinary tract cancer, lymphatic cancer,
        stomach cancer, renal cancer, colon cancer, larynx cancer, lung cancer and bone
        cancer, epidermoid tumors, squamous tumors, colorectal tumors, prostate tumors,
        breast tumors, lung tumors, pancreatic tumors, thyroid tumors, ovarian tumors,
        liver tumors, squamous cell carcinoma, basal cell carcinoma, human malignant
        keratinocytes, Kaposi's sarcoma, neuroblastomas, capillary hemangioblastomas,
        meningiomas, cerebral metastases, melanoma, gastrointestinal and renal

carcinomas and sarcomas, rhabdomyosarcoma, glioblastoma multiforme, histiocytic lymphoma, and leiomyosarcoma. neovascular glaucoma, proliferative retinopathy, diabetic retinopathy, retrolental fibroplastic retinopathy, macular degeneration, corneal graft rejection, atherosclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, Chron's disease, autoimmune nephritis, primary biliary cirrhosis, psoriasis, acute pancreatitis, allograph rejection, allergic inflammation, contact dermatitis, delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, hemangiomas, angiofibromas, Osler-Weber syndrome, restinosis, fungal, parasitic and viral infections, breast carcinoma, lung carcinoma, colorectal carcinoma, pancreatic carcinoma, glioma, lymphoma, leukemia, multiple myeloma, lymphoma, acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, erythrocytic leukemia, monocytic leukemia, Hodgkin's lymphoma and non-Hodgkin's lymphoma.

41.     A method of inhibiting VEGF receptors in a mammalian patient by administering to a mammalian patient a pharmaceutical composition comprising a compound of Formula (I) as defined in claim 1 and a pharmaceutical carrier.

42.     A method of treating cancer comprising administering to a patient afflicted with cancer a therapeutically effective amount of a compound of Formula (I) as defined in claim 1.

43.     The method of claim 42 wherein the therapeutically beneficial effect derives from inhibition of angiogenesis.

44.     The method of claim 43 wherein inhibition of angiogenesis is caused by inhibition of VEGF receptor tyrosine kinase activity in cells adjacent to the cancer.